2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of nickel. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Several different nickel compounds will be discussed in this profile. These compounds can be grouped according to their solubility in water: soluble compounds include nickel chloride, nickel sulfate, and nickel nitrate, and less-soluble compounds include nickel oxide and nickel subsulfide. Both the soluble and less-soluble nickel compounds are important with regard to all relevant routes of exposure. Generally, the soluble compounds are considered more toxic than the less-soluble compounds, although the less-soluble compounds are more likely to be carcinogenic at the site of deposition. Metallic nickel is also considered in this profile. All doses are presented as the amount or concentration of nickel to which subjects were exposed. Nickel carbonyl, a highly toxic nickel compound, is not considered in this profile. The data regarding the toxicity of nickel carbonyl are substantial; however, the likelihood of exposure at hazardous waste sites is very low. In ambient air, nickel carbonyl is relatively unstable with a half-life of ≈100 seconds (Stedman and Hikade 1980). Because nickel carbonyl is highly reactive, it is not likely to be found at hazardous waste sites. Also, nickel carbonyl is not very soluble in water; therefore, it will not be found in drinking water.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological,

neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowestobserved-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike,

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of nickel are indicated in Table 2-l and Figure 2-l. Because cancer effects could occur at lower exposure levels,

2. HEALTH EFFECTS

Figure 2-l also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 ($10m^{-4}$ to $l0^{-7}$), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for nickel. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or result from repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1 .I Death

Death from adult respiratory distress syndrome was reported in one person who sprayed nickel with a metal arc process without wearing personal protective equipment (Rendall et al. 1994). Several days after the exposure, urinary concentrations of nickel were 700 μg/L, in comparison to levels of <0.1-13.3 μg/L in persons not occupationally exposed to nickel (Sunderman 1993). The death occurred 13 days after the 90minute exposure to an estimated concentration of 382 mg nickel/m^3

of principally metallic nickel with the majority of particle sizes less than 1.4 pm. Histological examination of the lungs revealed alveolar wall damage and edema in alveolar spaces, and in the kidneys marked tubular necrosis was noted.

Human data regarding chronic inhalation exposure to nickel are limited to occupational exposure studies. The majority of these studies analyzed the toxicity of nickel, usually in the form of nickel oxide, metallic nickel, or nickel refinery dust, by calculating Standard Mortality Ratios (SMR) for all causes of death. Generally, the studies report a higher incidence of cancer deaths from lung and nasal cancers in the exposed workers (see Section 2.2.1.8). Two studies have also reported a higher incidence of deaths resulting from nonmalignant respiratory disease (Cornell and Landis 1984; Polednak 1981). However, all of the workers were exposed to other metals (arsenic, uranium, iron, lead, chromium), so it cannot be concluded that nickel was the sole causative agent. Other studies of humans occupationally exposed to nickel compounds have not reported increased mortality resulting from respiratory diseases (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh 1982; Redmond 1984; Shannon et al. 1984b, 1991).

During the first 2 days after a single 2-hour exposure, 4 of 28 rats died after exposure to nickel sulfate at 36.5 mg nickel/m^3 (Hirano et al. 1994b). Severe hemorrhage of the lungs was observed in the lungs of the rats that died. During inhalation exposure of 6 hours/day, 5 days/week, for up to 12 exposures, rats and mice exposed to nickel sulfate and nickel subsulfide died but not those exposed to nickel oxide (Benson et al. 1987, 1988; Dunnick et al. 1988). Mice were more sensitive to lethality than rats; at 1.6 mg nickel/m^3 as nickel sulfate, all mice and no rats died, and at 7.3 mg nickel/m^3 as nickel subsulfide, all mice and 2 of 10 rats died. No rats or mice died following exposure to 23.6 mg nickel/m^3 as nickel oxide. No deaths were reported in rats or mice following 13 weeks of exposure (6 hours/day, 5 days/week) to nickel at 7.9, 1.8, or 0.4 mg nickel/m^3 as nickel oxide, nickel subsulfide, or nickel sulfate, respectively (Dunnick et al. 1989). Hamsters survived exposure to 148.4 mg nickel/m^3 as nickel oxide for 15 or 61 days (Wehner and Craig 1972).

Significant mortality was observed during the last 26 weeks of a 78-week inhalation study of rats exposed to 0.7 mg nickel/m^3 as nickel subsulfide (Ottolenghi et al. 1974). Less than 5% of the treated rats survived the study (78 weeks of exposure plus 30 weeks of observation) compared to 31% of the controls (Ottolenghi et al. 1974). All rats, guinea pigs, and mice exposed to 15 mg

nickel/m^3 as metallic nickel for ≤21 months died before the end of the study, with most of the guinea pigs and mice dying by 15 months (Hueper 1958). Lung lesions including edema, hyperemia, and hemorrhage were the principal effects noted. However, no controls were used in this study. A significant decrease in mean survival time was observed in rats exposed 23 hours/day for life to 0.06 mg nickel/m^3 as nickel oxide (Takenaka et al. 1985). The average survival time for rats exposed to 0 or 0.06 mg nickel/m^3 was 125.2 and 87.7 weeks, respectively. Survival was not affected in rats exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg nickel/m^3, respectively, for 104 weeks (Dunnick et al. 1995; NTP 1996a, 1996b, 1996c). Survival of mice was also not affected by exposure to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, for 104 weeks (Dunnick et al. 1995; NTP 1996a, 1996b, 1996c).

LOAEL values from each reliable study for death in each species, duration category, and nickel compound are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

No studies were located regarding ocular effects in humans or animals after inhalation exposure to nickel. Other systemic effects are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species, duration category, and nickel compound are recorded in Table 2-l and plotted in Figure 2-l.

Respiratory Effects. Studies in both humans and animals indicate that the respiratory system is the primary target of nickel toxicity following inhalation exposure. A single case of death from adult respiratory distress syndrome has been reported following exposure for 90 minutes to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al.1994).

Histological changes noted in the lungs of this case included alveolar wall damage, with fibrotic changes, and edema in the alveolar space. An increased incidence in deaths from respiratory disease was found in workers chronically exposed to ≥0.04 mg nickel/m^3, usually as nickel oxide or metallic nickel (Cornell and Landis 1984; Polednak 1981). The increase in the Polednak (1981) study was not statistically significant. Respiratory effects in the workers included chronic bronchitis, emphysema, and reduced vital capacity. The workers were also exposed to a variety of other metals, including arsenic, uranium, iron, lead, and chromium, so it cannot be

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
ACUTE EXPOSURE							
Death							
1	Human	90 min				382 M (death of one man from adult respiratory distress syndrome)	Rendall et al. 1994 metal
2	Rat (Fischer- 344)	12 d 5d/wk 6hr/d				7.3 (1/10 died)	Benson et al. 1987; Dunnick et al. 1988; NTP 1996b subsulfide
3	Rat (Fischer- 344)	12 d 5d/wk 6hr/d				6.7 (2/10 died)	Benson et al. 1988; Dunnick et al. 1988; NTP 1996c sulfate
4	Rat (Wistar)	2 hr				36.5 M (4/28 died)	Hirano et al. 1994b sulfate
5	Mouse (B6C3F1)	12 d 5d/wk 6hr/d				7.3 (10/10 died)	Benson et al. 1987; Dunnick et al. 1988; NTP 1996b subsulfide
6	Mouse (B6C3F1)	12 d 5d/wk 6hr/d				1.6 (10/10 died)	Benson et al. 1988; Dunnick et al. 1988; NTP 1996c sulfate

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
	Systemic						
7	Rat (Fischer- 344)	12 d 5d/wk 6hr/d	Resp			0.4 (pneumonia; atrophy of olfactory epithelium)	Benson et al. 1987; Dunnick et al. 1988; NTP 1996b subsulfide
			Cardio	7.3			
			Gastro	7.3			
			Musc/skel	7.3			
			Hepatic	7.3			
			Renal	7.3			
			Endocr	7.3			
			Derm	7.3			
			Bd Wt	1.8		3.6 (body weights 23-29% lower than controls)	
8	Rat (Fischer- 344)	12 d 5d/wk 6hr/d	Resp			0.8 (labored breathing; pneumonia; degeneration of respiratory epithelium and atrophy of olfactory epithelium)	Benson et al. 1988; Dunnick et al. 1988; NTP 1996c sulfate
			Cardio	13.3			
			Gastro	13.3			
			Musc/skel	13.3			
			Hepatic	13.3			
			Renal	13.3			
			Endocr	13.3			
			Derm	13.3			
			Bd Wt			0.8 M (body weights 28% lower than controls, emaciation)	
9	Rat (Fischer- 344)	1, 2, 4, 7, 12 d 6hr/d	Resp		0.22 (alveolitis)		Benson et al. 1995b subsulfide

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)		Serious (mg Ni/m^3)		Reference/ Chemical form
10	Rat (Fischer- 344)	12 d 5d/wk 6hr/d	Resp	2.0	3.9	(alveolar macrophage hyperplasia)	23.6	(pneumonia; atrophy of olfactory epithelium)	Dunnick et al. 1988; NTP 1996a oxide
			Cardio	23.6					
			Gastro	23.6					
			Musc/skel	23.6					
			Hepatic	23.6					
			Renal	23.6					
			Endocr	23.6					
			Derm	23.6					
			Bd Wt	23.6					
11	Mouse (B6C3F1)	12 d 5d/wk 6hr/d	Resp	0.4			0.9	(pneumonia; atrophy of the olfactory epithelium; degeneration of the respiratory epithelium)	Benson et al. 1987; Dunnick et al. 1988; NTP 1996b subsulfide
			Cardio	3.6					
			Gastro	3.6					
			Musc/skel	3.6					
			Hepatic	3.6					
			Renal	3.6					
			Endocr	3.6					
			Derm	3.6					
			Bd Wt	1.8	3.6	(body weights 10-14% less than controls)			

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)		Serious (mg Ni/m^3)		Reference/ Chemical form
12	Mouse (B6C3F1)	12 d 5d/wk 6hr/d	Resp				0.8	(lung inflammation; atrophy of the olfactory epithelium)	Benson et al. 1988; Dunnick et al. 1988; NTP 1996c sulfate
			Cardio	0.8					
			Gastro	0.8					
			Musc/skel	0.8					
			Hepatic	0.8					
			Renal	0.8					
			Endocr	0.8					
			Derm	0.8					
			Bd Wt	0.8					
13	Mouse (B6C3F1)	12 d 5d/wk 6hr/d	Resp	3.9	7.9	(alveolar macrophage hyperplasia)	23.6	(lung inflammation)	Dunnick et al. 1988; NTP 1996a oxide
			Cardio	23.6					
			Gastro	23.6					
			Musc/skel	23.6					
			Hepatic	23.6					
			Renal	23.6					
			Endocr	23.6					
			Derm	23.6					
			Bd Wt	23.6					
Immuno/Lymphor									
14	Rat (Fischer- 344)	12 d 5d/wk 6hr/d		7.9	23.6	(atrophy of the thymus; hyperplasia of lymph nodes)			Dunnick et al. 1988; NTP 1996a oxide
15	Mouse (CD-1)	2 hr			0.46 F	(increased susceptibility to streptococcal infection)			Adkins et al. 1979 chloride or sulfate

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)		Serious (mg Ni/m^3)		Reference/ Chemical form
16	Mouse (B6C3F1)	12 d 5d/wk 6hr/d		7.9	23.6	(atrophy of the thymus; hyperplasia of the lymph nodes)			Dunnick et al. 1988; NTP 1996a oxide
17	Mouse (Swiss)	2 hr		0.1 F	0.25 F	(decrease in the number of antibody-producing spleen cells)			Graham et al. 1978 chloride
	Neurological								
18	Rat (Fischer- 344)	12 d 5d/wk 6hr/d		23.6					Dunnick et al. 1988; NTP 1996a oxide
19	Mouse (B6C3F1)	12 d 5d/wk 6hr/d		23.6					Dunnick et al. 1988; NTP 1996a oxide
INTERMEDIATE EXPOSURE									
	Systemic								
20	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d	Resp		0.4 M	(alveolar macrophage hyperplasia; increased relative lung weights)	2	(chronic active inflammation of the lungs)	Benson et al. 1989; Dunnick et al. 1989; NTP 1996a oxide
			Hepatic	7.9					
			Renal	7.9					
			Bd Wt	7.9					

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
21	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d	Resp		0.11 (alveolar macrophage hyperplasia; increased relative lung weights)	0.2 (chronic active inflammation of the lungs)	Benson et al. 1989; Dunnick et al. 1989; NTP 1996b subsulfide
			Hepatic	1.8			
			Renal	1.8			
			Bd Wt	1.8			
22	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d	Resp		0.03 (alveolar macrophage hyperplasia)		Benson et al. 1989; Dunnick et al. 1989; NTP 1996c sulfate
			Hepatic	0.44			
			Renal	0.44			
			Bd Wt	0.44			
23	Rat (Fischer- 344)	up to 6 mo 5d/wk 6hr/d	Resp	0.49 M		1.96 M (moderate alveolitis that persisted at least 4 months after the exposure)	Benson et al. 1995a oxide
			Bd Wt	1.96 M			
24	Rat (Fischer- 344)	up to 6 mo 5d/wk 6hr/d	Resp		0.03 M (reversible macrophage hyperplasia)		Benson et al. 1995a sulfate
25	Rat (Wistar)	1 mo 5d/wk 6hr/d	Resp		0.5 M (bronchial gland hyperplasia 20 months after the end of exposure)		Horie et al. 1985 oxide

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
26	Rat (Wistar)	28 d 23.6 hr/d	Resp		0.2 M (increased lung weight)		Weischer et al. 1980 oxide
			Hemato		0.2 M (decreased hematocrit)		
			Hepatic	0.4 M	0.8 M (decreased liver weight)		
			Renal	0.8 M			
			Bd Wt	0.2 M		0.4 M (30% decrease in body weight gain)	
			Metabolic	0.2 M	0.4 M (increased serum glucose)		
27	Rat (Wistar)	21 d 23.6 hr/d	Resp		0.8 F (increased lung weight)		Weischer et al. 1980 oxide
			Hemato		0.8 F (increased hematocrit)		
			Hepatic		0.8 F (decreased liver weight)		
			Renal		0.8 F (decreased kidney weight)		
			Bd Wt			0.8 F (36% decrease in body weight gain)	
			Metabolic		0.8 F (hypoglycemia)		
28	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d	Resp		2.0 (alveolar macrophage hyperplasia)	7.9 (chronic active inflammation of the lungs)	Benson et al. 1989; Dunnick et al. 1989; NTP 1996a oxide
			Hepatic	7.9			
			Renal	7.9			
			Bd Wt	7.9			

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)		LOAEL (effect) Serious (mg Ni/m^3)		Reference/ Chemical form
29	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d	Resp	0.11	0.2	(alveolar macrophage hyperplasia)	0.9	(chronic active inflammation of the lungs; fibrosis)	Benson et al. 1989; Dunnick et al. 1989; NTP 1996b subsulfide
			Hepatic	1.8					
			Renal	1.8					
			Bd Wt	1.8					
30	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d	Resp	0.06	0.11	(alveolar macrophage hyperplasia)	0.44	(chronic active inflammation of the lungs; fibrosis)	Benson et al. 1989; Dunnick et al. 1989; NTP 1996c sulfate
			Hepatic	0.44					
			Renal	0.44					
			Bd Wt	0.44					
31	Mouse (B6C3F1)	up to 6mo 5d/wk 6hr/d	Resp		0.98 M	(interstitial pneumonia)			Benson et al. 1995a oxide
			Bd Wt	3.93 M					
32	Mouse (B6C3F1)	up to 6mo 5d/wk 6hr/d	Resp	0.06 M	0.22 M	(interstitial pneumonia)			Benson et al. 1995a sulfate
33	Rabbit (NS)	1-8 mo 5d/wk 6hr/d	Resp		0.2 M	(increased volume density of alveolar type II cells)			Johansson and Camner 1986 chloride or metallic
Immuno/Lymphor									
34	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d		0.11	0.22	(mild lymphoid hyperplasia)			Dunnick et al. 1989; NTP 1996c sulfate

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
35	Rat (Wistar)	4 mo continuous		0.025	0.15 (decrease in the number of macrophages; decreased antibody production)		Spiegelberg et al. 1984 oxide
36	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d		0.22	0.44 (mild lymphoid hyperplasia)		Dunnick et al. 1989 sulfate
37	Mouse (B6C3F1)	65 d 5d/wk 6hr/d		0.11 F	0.45 F (decreased alveolar macrophage phagocytic activity)		Haley et al. 1990 subsulfide
38	Mouse (B6C3F1)	65 d 5d/wk 6hr/d		0.11 F		0.45 F (decreased resistance to tumor challenge)	Haley et al. 1990 sulfate
39	Mouse (B6C3F1)	65 d 5d/wk 6hr/d			0.47 F (decreased alveolar macrophage activity)		Haley et al. 1990 oxide
	Reproductive						
40	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d		3.9 M	7.9 M (21% decreased sperm numbers)		Dunnick et al. 1989; NTP 1996a oxide
41	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d		1.8			Dunnick et al. 1989; NTP 1996b subsulfide
42	Rat (Fischer- 344)	13 wk 5d/wk 6hr/d		0.44			Dunnick et al. 1989; NTP 1996c sulfate

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
43	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d		7.9			Dunnick et al. 1989; NTP 1996a oxide
44	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d		1.8			Dunnick et al. 1989; NTP 1996b subsulfide
45	Mouse (B6C3F1)	13 wk 5d/wk 6hr/d		0.44			Dunnick et al. 1989; NTP 1996c sulfate
	Developmental						
46	Rat (Wistar)	Gd 1-21 23.6 hr/day		0.8	1.6 (decreased fetal body weights)		Weischer et al. 1980 oxide
	CHRONIC EXPOSURE						
	Death						
47	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d				0.7 (<11/226 survived)	Ottolenghi et al. 1974 subsulfide
48	Rat (Wistar)	31 mo 7d/wk 23hr/d				0.06 M (decreased survival time; control - 125.2 wk; 0.06 mg/m^3 - 87.7 wk)	Takenaka et al. 1985 oxide
49	Gn pig (strain 13)	21 mo 4-5d/wk 6hr/d				15 (42/42 died)	Hueper 1958 metallic

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
Systemic							
50	Human	occupa-tional	Renal			0.75 F (increased urinary excretion of *N*-acetyl-β-D-glucosamidase, total proteins, β_2 -microglobulin, and retinol binding protein)	Vyskocil et al. 1994a sulfate, chloride
51	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d	Resp		0.5 (minimal to mild chronic active inflammation of the lungs)	1 (mild to moderate chronic active inflammation of the lungs)	Dunnick et al. 1995; NTP 1996a oxide
			Cardio	2			
			Gastro	2			
			Hemato	2			
			Hepatic	2			
			Renal	2			
			Endocr	1	2 F (adrenal medulla hyperplasia)		
			Derm	2			
			Bd Wt	2			

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)		Serious (mg Ni/m^3)		Reference/ Chemical form
52	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d	Resp				0.11	(mild to moderate chronic active inflammation; minimal to mild fibrosis)	Dunnick et al. 1995; NTP 1996b subsulfide
			Cardio	0.73					
			Gastro	0.73					
			Hemato	0.11	0.73	(increased hematocrit associated with mild dehydration)			
			Hepatic	0.73					
			Renal	0.73					
			Endocr	0.11		F (adrenal medulla hyperplasia)			
			Derm	0.73					
			Bd Wt	0.11		dy weight 11-12% than controls during ar)			
53	Rat (Fischer 344)	2 yr 5d/wk 6hr/d	Resp	0.03[b]	0.0	o mild chronic mation and lungs)			Dunnick et al. 1995; NTP 1996c sulfate
			Cardio	0.11					
			Gastro	0.11					
			Hemato	0.11					
			Hepatic	0.11					
			Renal	0.11					
			Endocr	0.11					
			Derm	0.11					
			Bd Wt	0.11					

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
54	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d	Resp			0.7 (pneumonitis; bronchitis; emphysema)	Ottolenghi et al. 1974 subsulfide
			Cardio	0.7			
			Gastro	0.7			
			Hepatic	0.7			
			Renal	0.7			
			Endocr	0.7			
			Bd Wt			0.7 (body weight 20-30% less than controls)	
55	Rat (Wistar)	31 mo 7d/wk 23hr/d	Resp			0.06 M (increased lung weight; congestion; alveolar proteinosis)	Takenaka et al. 1985 oxide
			Bd Wt		0.06 M (weight loss amount not stated)		
56	Rat (Wistar)	12 mo 5d/wk 7hr/d	Resp			0.2 (pneumonia)	Tanaka et al. 1988 oxide
			Hepatic	0.9			
			Renal	0.9			
			Bd Wt	0.9			

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
57	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d	Resp		1 (minimal to mild chronic active inflammation of the lungs)		Dunnick et al. 1995; NTP 1996a oxide
			Cardio	3.9			
			Gastro	3.9			
			Hemato	3.9			
			Hepatic	3.9			
			Renal	3.9			
			Endocr	3.9			
			Derm	3.9			
			Bd Wt	3.9			
58	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d	Resp		0.44 (minimal fibrosis; minimal to mild chronic active inflammation)		Dunnick et al. 1995; NTP 1996b subsulfide
			Cardio	0.88			
			Gastro	0.88			
			Hemato	0.88			
			Hepatic	0.88			
			Renal	0.88			
			Endocr	0.88			
			Derm	0.88			
			Bd Wt	0.44	0.88 F (body weights 14% lower than controls)		

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
59	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d	Resp		0.06 F (minimal to mild chronic active inflammation and alveolar epithelial hyperplasia)		Dunnick et al. 1995; NTP 1996c sulfate
			Cardio	0.22			
			Gastro	0.22			
			Hemato	0.22			
			Hepatic	0.22			
			Renal	0.22			
			Endocr	0.22			
			Derm	0.22			
			Bd Wt	0.11	0.22 F (body weights 12% lower than controls during the 2nd year)		
Immuno/Lymphor							
60	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		0.06	0.11 (bronchial lymph node hyperplasia)		NTP 1996c sulfate
61	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		0.11	0.22 (bronchial lymph node hyperplasia)		NTP 1996c sulfate
Neurological							
62	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		2			NTP 1996a oxide
63	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		3.9			NTP 1996a oxide

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)	Reference/ Chemical form
Reproductive							
64	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d		2			NTP 1996a oxide
65	Mouse (B6C3F1)	2 yr 5d/wk 6hr/d		3.9			NTP 1996a oxide
Cancer							
66	Human	occupa-tional				>10 M (CEL: lung and nasal cancers)	Int Committee on Ni Carcinogenesis in Man 1990 less soluble
67	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d				1 (CEL: 12/106 alveolar/bronchiolar adenoma or carcinoma) 2 (CEL: 53/108 benign or malignant pheochromocytoma of the adrenal medulla)	Dunnick et al. 1995; NTP 1996a oxide
68	Rat (Fischer- 344)	2 yr 5d/wk 6hr/d				0.11 (CEL: 12/106 alveolar/bronchial adenoma carcinoma) 0.11 M (CEL: 30/53 benign or malignant pheochromocytoma of the adrenal medulla)	Dunnick et al. 1995; NTP 1996b subsulfide

TABLE 2-1. Levels of Significant Exposure to Nickel - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (mg Ni/m^3)	LOAEL (effect) Less serious (mg Ni/m^3)	LOAEL (effect) Serious (mg Ni/m^3)		Reference/ Chemical form
69	Rat (Fischer- 344)	78 wk 5d/wk 6hr/d				0.7	(CEL: lung adenomas, adenocarcinomas, squamous cell carcinoma, 14% treated, 1% controls)	Ottolenghi et al. 1974 subsulfide

[a]The numbers correspond to entries in Figure 2-1.

[b]Used to derive a chronic inhalation Minimal Risk Level (MRL) of 2 x 10^{-4}mg/m^3 nickel for soluble nickel salts; dose adjusted for intermittent exposure (6/24 hours, 5/7 days), multiplied by the Regional Deposited Dose Ratio (0.9714 for pulmonary region deposition; mass median aerodynamic diameter [MMAD] = 2.5 μm, sigma = 2.4 μm), and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cadiovascular; CEL = cancer effect level; d = day(s); Derm = dermal; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphor = immunological lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculoskeletal; Ni = nickel; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Nickel – Inhalation

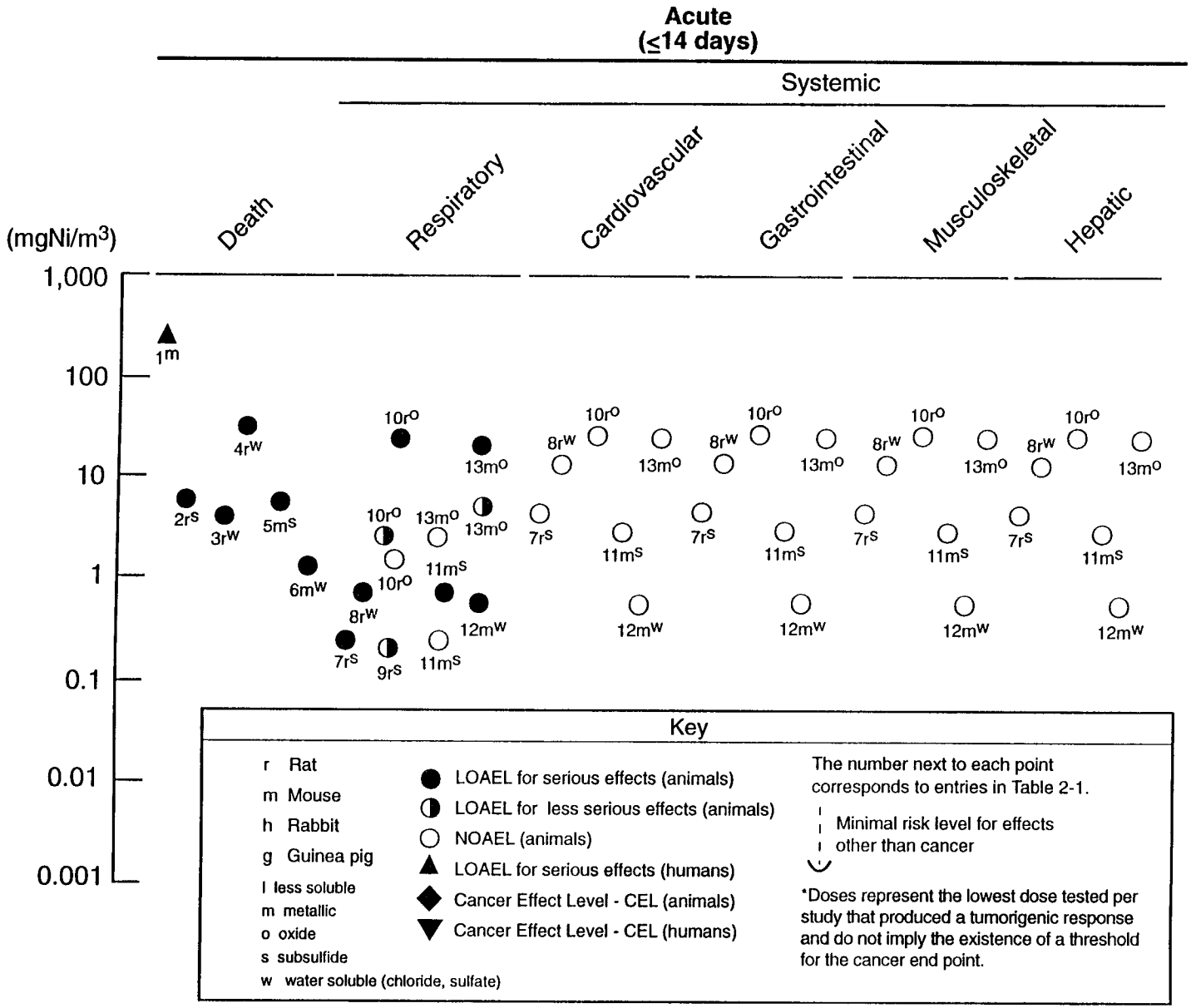


Figure 2-1. Levels of Significant Exposure to Nickel – Inhalation

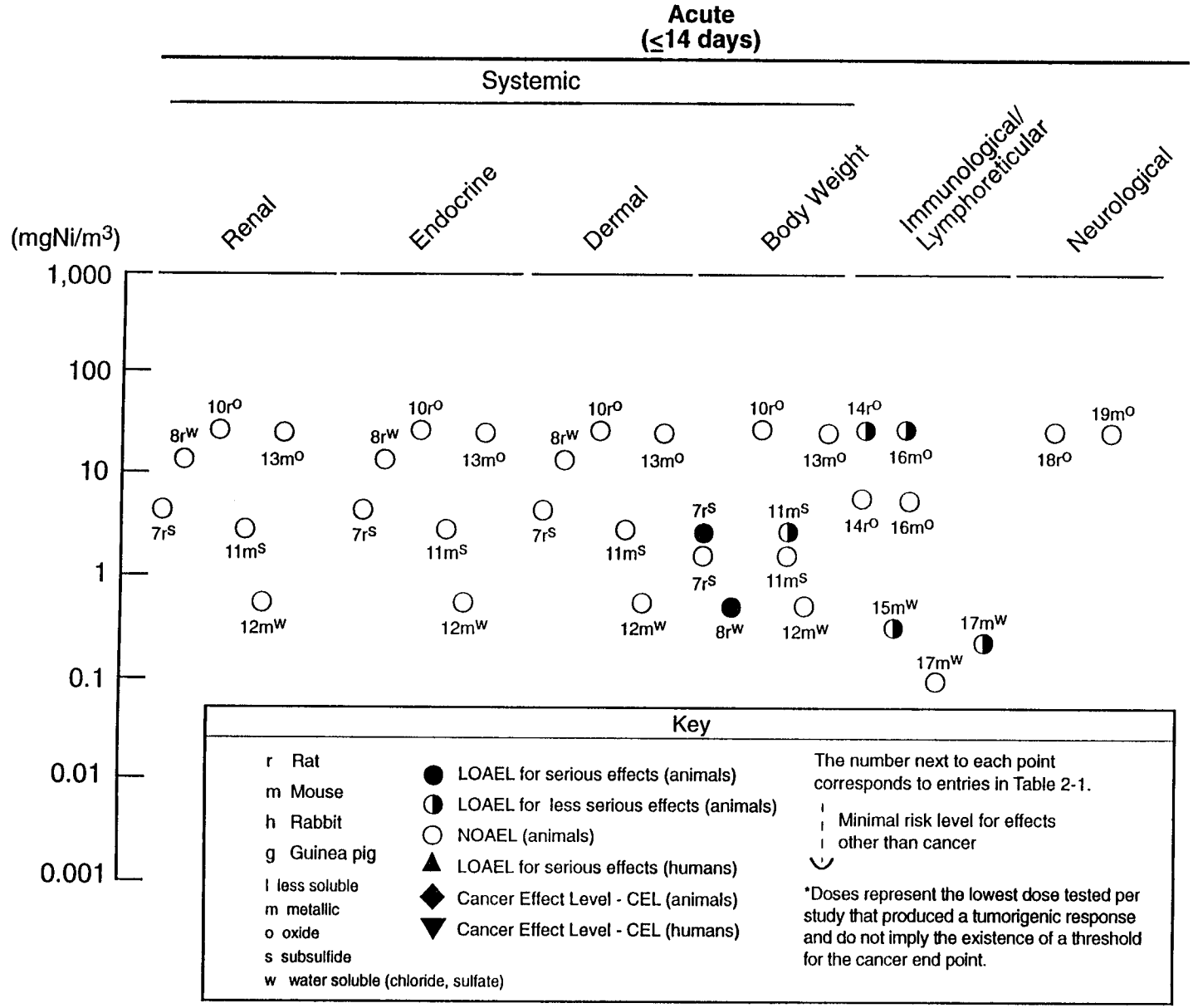


Figure 2-1. Levels of Significant Exposure to Nickel – Inhalation (continued)

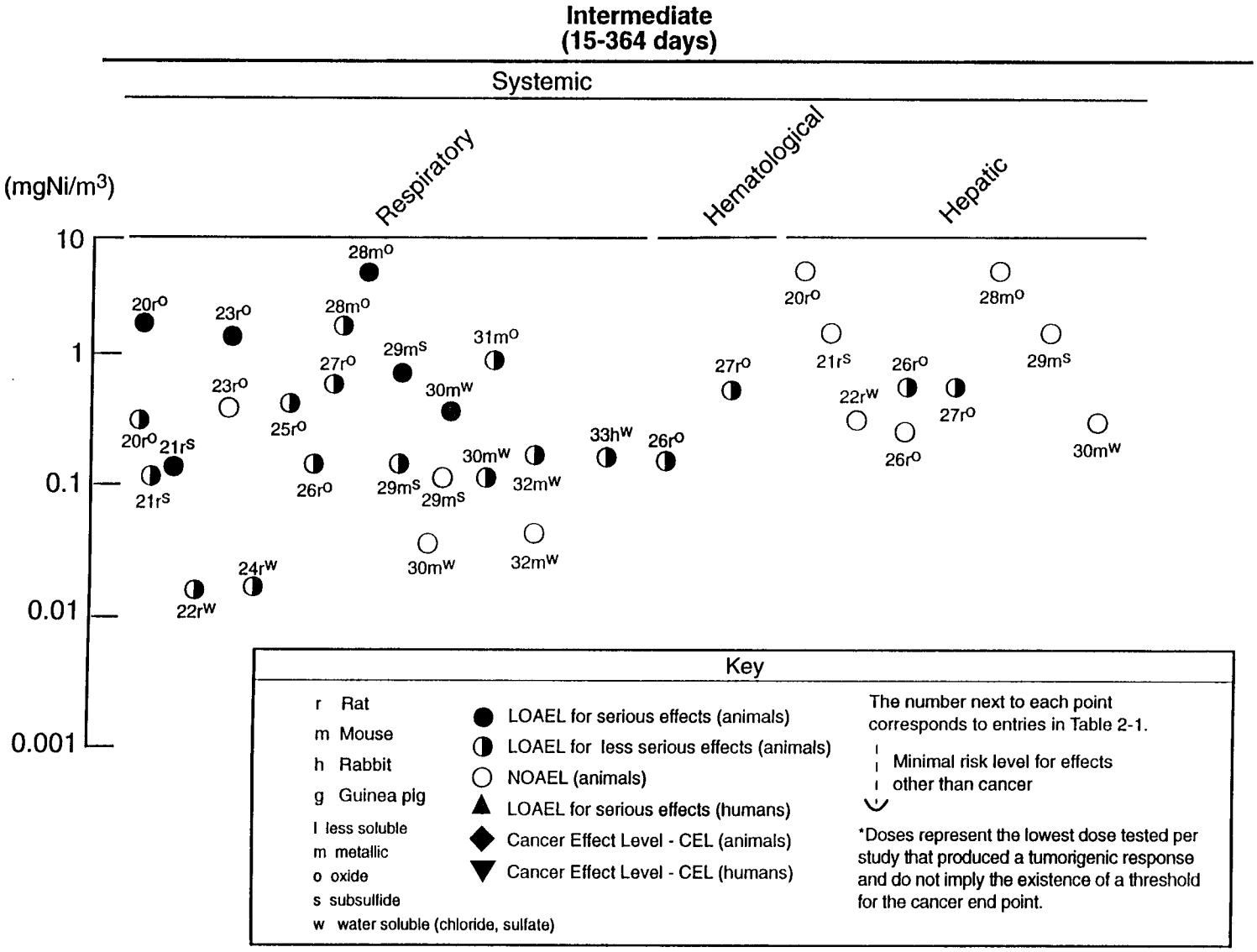


Figure 2-1. Levels of Significant Exposure to Nickel – Inhalation (continued)

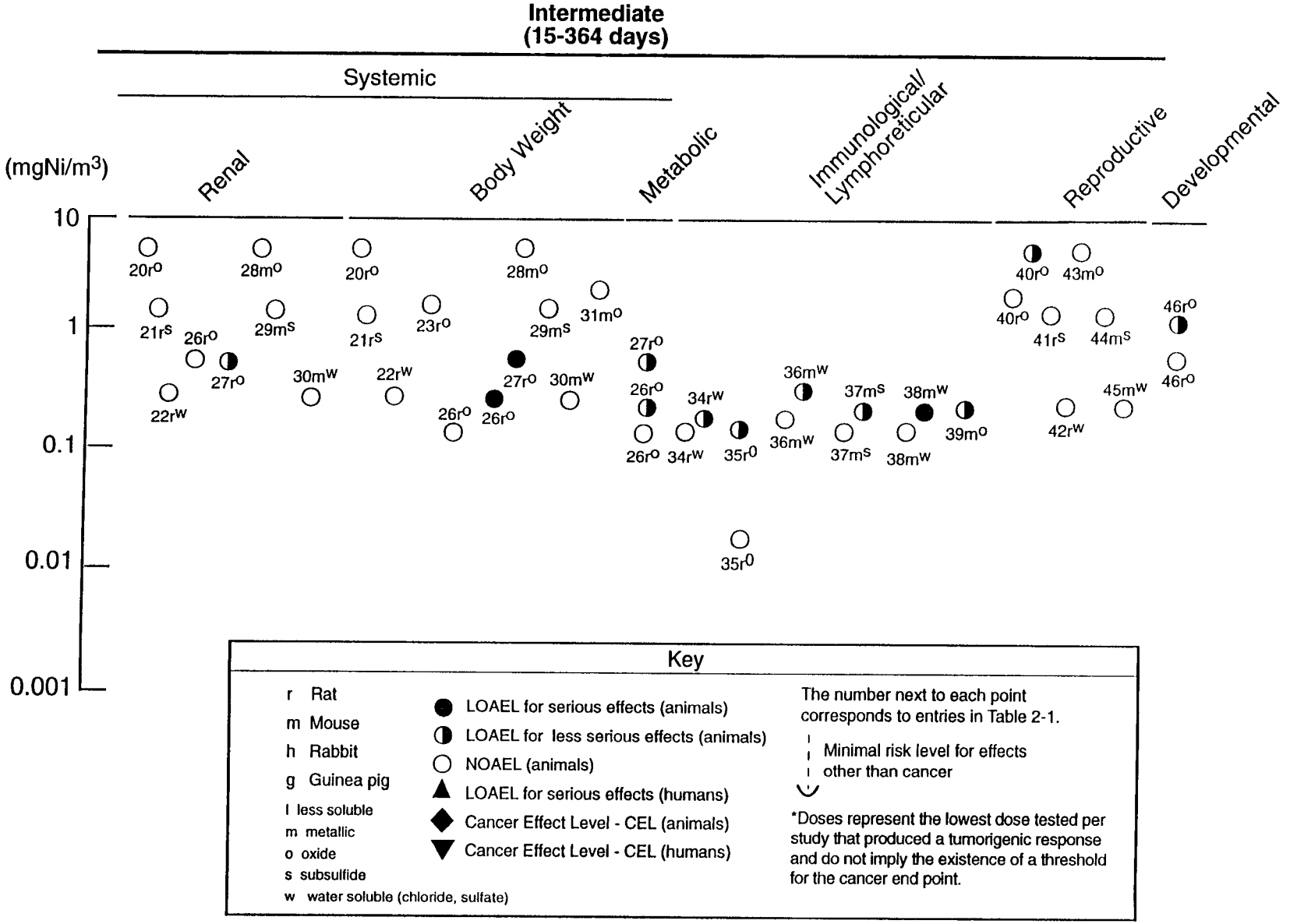


Figure 2-1. Levels of Significant Exposure to Nickel – Inhalation (continued)

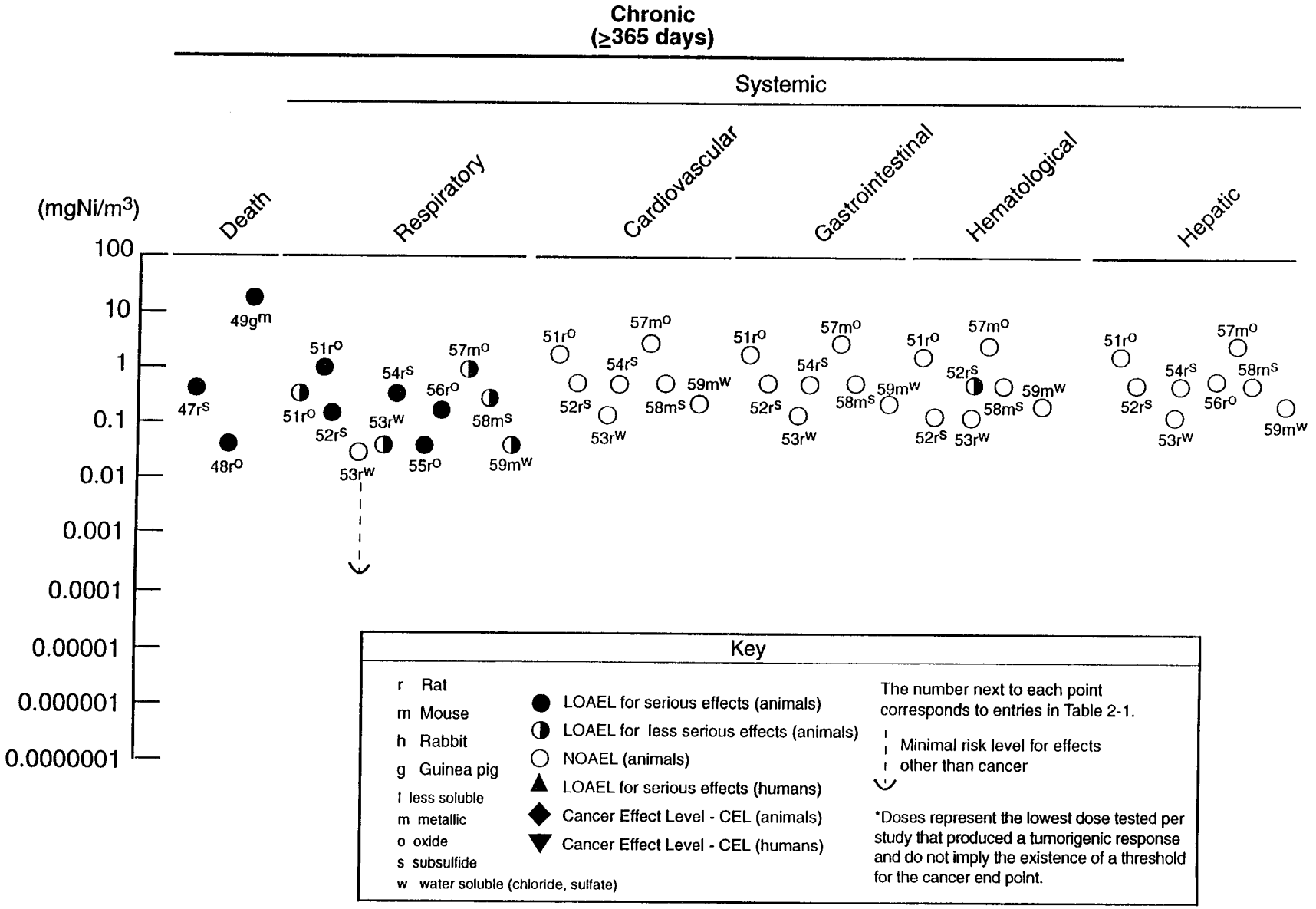
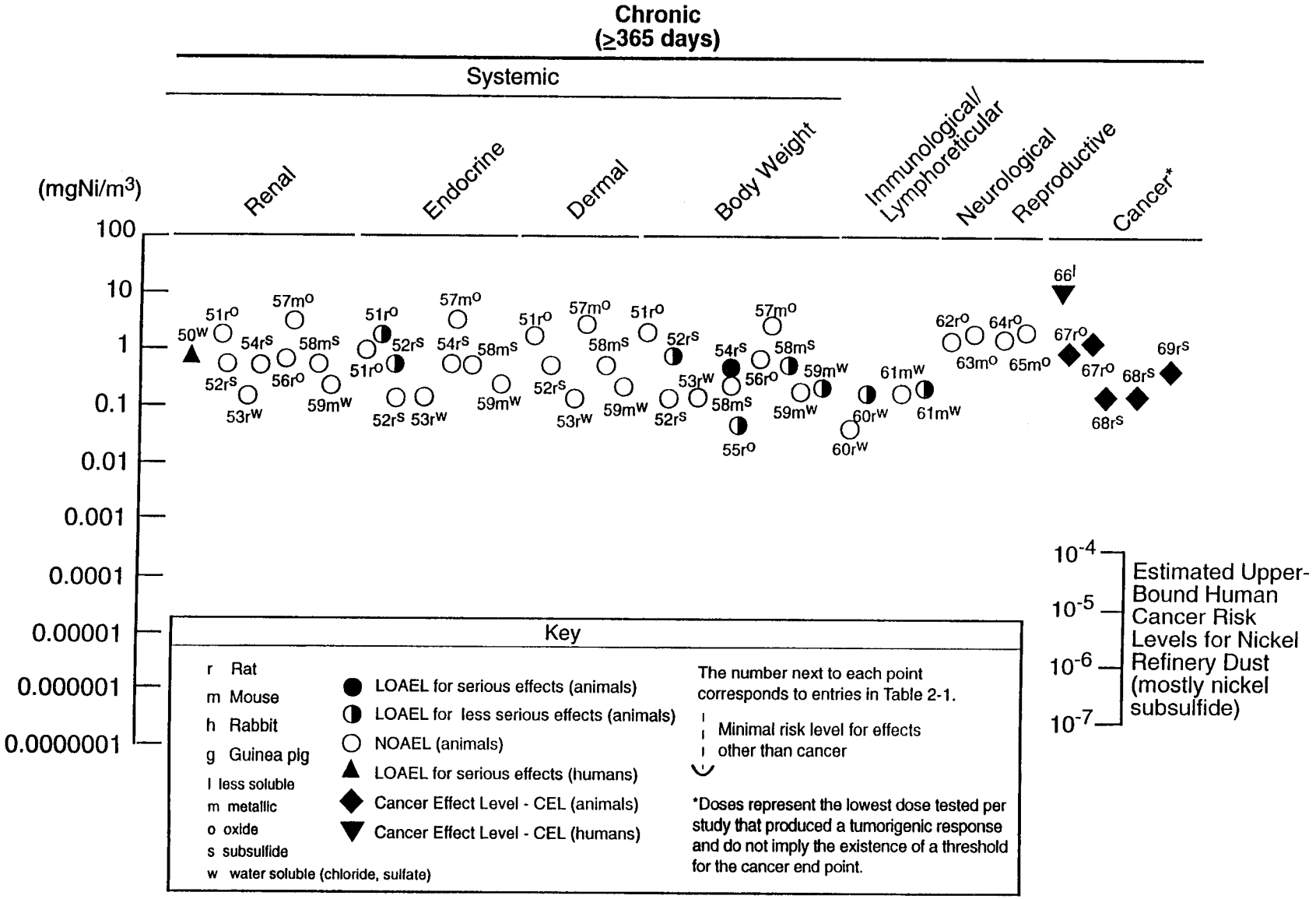


Figure 2-1. Levels of Significant Exposure to Nickel – Inhalation (continued)



concluded that nickel was the sole causative agent. Other studies have not shown increases in the incidence of deaths from respiratory disease (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh 1982; Redmond 1984; Shannon et al. 1984b, 1991). Reduced vital capacity and expiratory flows were observed in stainless steel welders (Kilbum et al. 1990). Alveolar volume and total thoracic gas volume were unaffected. Because the welders were also exposed to high levels of chromium, the role of nickel in the etiology of the impaired lung function is not known, and the study authors concluded that there is little evidence for adverse chronic effects on pulmonary function caused by nickel. Asthma induced by occupational exposure to nickel has been documented (Dolovich et al. 1984; Novey et al. 1983; Shirakawa et al. 1990). The asthma can result from either primary irritation or from an allergic response. Examination of chest radiographs of nickel sinter plant workers exposed to nickel at concentrations as high as 100 ng/m^3 did not reveal an increase in small irregular opacities (Muir et al. 1993). This study suggests that nickel does not result in an inflammatory or fibrogenic response in the lungs of occupationally exposed individuals.

Numerous studies in animals have investigated the respiratory effects of nickel exposure. Intermittent exposure (6 hours/day, 5 days/week) of rats and mice for 16 days or 13 weeks resulted in chronic active inflammation in the lungs, fibrosis, macrophage hyperplasia, interstitial infiltrates, and increased lung weight following exposure to ≥0.06 mg nickel/m^3 as nickel sulfate, ≥0.11 mg nickel/m^3 as nickel subsulfide, and ≥0.4 mg nickel/m^3 as nickel oxide (Benson et al. 1987, 1988, 1989; Dunnick et al. 1988, 1989). Olfactory epithelial atrophy of the nose was also reported following exposure to nickel sulfate and nickel subsulfide but not nickel oxide. Rats appeared to be more sensitive to the respiratory effects of nickel than mice. The toxicity depended on the solubility of the compounds and not on lung burden since the compound with the lowest toxicity (nickel oxide) resulted in the highest lung burden. The studies indicate the following toxicity ranking: nickel sulfate > nickel subsulfide > nickel oxide.

In a study of the time course of nickel-induced respiratory lesions, rats were exposed at 0, 0.22, or 0.95 mg nickel/m^3 as nickel subsulfide 6 hours/day for up to 22 days (Benson et al. 1995b). Inflammatory lung lesions peaked at day 4 of exposure at the high concentration. Alveolitis was noted at the low concentration in all six exposed rats after 7 days of exposure (rats exposed to the low concentration were not examined at earlier time points). Following 6 months of exposure (6 hours/day, 5 days/week), alveolitis of moderate severity was observed in rats exposed to nickel

oxide at 1.96 mg nickel/m^3, and mild alveolitis was observed in rats exposed to nickel sulfate at 0.11 mg nickel/m^3 (Benson et al. 1995a). In mice, interstitial pneumonia was observed at 0.98 mg nickel/m^3 and 0.22 mg nickel/m^3 following 6 months of exposure to nickel oxide and nickel sulfate, respectively (Benson et al. 1995a).

In a study designed specifically to examine the effects of nickel on the olfactory system, rats were exposed to nickel sulfate at 0 or 0.635 mg nickel/m^3 6 hours/day for 16 days (Evans et al. 1995). Histological changes in the olfactory epithelium of exposed rats included a slight reduction in the number of bipolar sensory receptor cells, a decrease in the thickness of the olfactory epithelium resulting from a loss of sustentacular cells, a thinning of apical cytoplasm, and a reduction in the number of sensory cilia on the surface of the cells. After a recovery period of 22 days, fewer sensory cilia was the only change that remained, indicating that the effects of an intermediate duration exposure to nickel were reversible.

Significantly increased lung weights were observed in rats exposed 23.6 hours/day to nickel oxide at 0.8 mg nickel/m^3 for 21 days, and at 0.2 mg nickel/m^3 for 28 days (Weischer et al. 1980). Microscopic examinations of the lungs were not completed in this study. Hyperplasia of the bronchial epithelium was observed in rats exposed intermittently to nickel chloride at 0.11 mg nickel/m^3 for up to 6 weeks (Bingham et al. 1972) and in rats examined 20 months after a l-month intermittent exposure to nickel oxide at 0.5 mg nickel/m^3 (Horie et al. 1985). Alveolar wall thickening was observed in rats exposed intermittently to 0.12 mg nickel/m^3 as nickel oxide for up to 6 weeks (Bingham et al. 1972). Pneumonia and bronchial epithelial metaplasia were observed in rats exposed intermittently for 1 year to 0.2 mg nickel/m^3 as nickel oxide (Tanaka et al. 1988).

An increase in lung lesions, as compared to controls, was observed in rats exposed to 0.7 mg nickel/m^3 as nickel subsulfide for 78 weeks (6 hours/day, 5 days/week), followed by a 30-week observation period (Ottolenghi et al. 1974). The lung lesions included pneumonitis, atelectasis, bronchitis, bronchiectasis, and emphysema. Morphological alterations in alveolar macrophages (hyperplasia and lamellated material in the cytoplasm) were associated with impaired cellular function in rabbits exposed to 20.2 mg nickel/m^3 as metallic nickel or nickel chloride for 18 months (Johansson and Camner 1986; Johansson et al. 1981). An increase in volume density of alveolar type II cells was also observed in rabbits exposed to 0.2 mg nickel/m^3 as metallic nickel or nickel chloride for 1 month (Johansson and Camner 1986; Johansson et al. 1981).

2. HEALTH EFFECTS

Alveolar proteinosis and marked increased lung weights were observed in rats exposed for life to 0.06 mg nickel/m^3 as nickel oxide (Takenaka et al. 1985). At the end of the 31-month experiment, two surviving rats (one at 0.06 mg/m^3, one at 0.2 mg/m3) also had focal fibrosis. Although the total number of rats surviving 31 months was not stated, it was less than 90% of the 40 rats exposed at 0.06 mg/m^3 and the 20 rats exposed at 0.2 mg/m^3. Pneumoconiosis was observed in hamsters following lifetime exposure to 42 mg nickel/m^3 as nickel oxide alone or in combination with cigarette smoke (Wehner 1986; Wehner et al. 1975, 1979). The pneumoconiosis was characterized by lung changes of interstitial pneumonitis, diffuse granulomatous inflammation, bronchial and bronchiolar epithelial hyperplasia, fibrosis of the alveolar septa, bronchiolization of the alveolar epithelium, and emphysema and/or atelectasis. The pneumoconiosis increased in severity as a function of exposure time and age. Emphysema was observed in the animals that died before developing pneumoconiosis.

In 2-year inhalation studies of nickel oxide, nickel subsulfide, and nickel sulfate in rats and mice, respiratory lesions observed for all compounds included increased lung weights, focal alveolar/ bronchiolar hyperplasia, inflammation and/or fibrosis of the lung, and lymphoid hyperplasia of the lung-associated lymph nodes (Dunnick et al. 1995; NTP 1996a, 1996b, 1996c). The investigators noted that qualitatively the inflammatory responses in the lungs were similar with all three compounds; however, the effects were more severe after exposure to nickel oxide and nickel subsulfide. In addition to lung effects, atrophy of the olfactory epithelium was also observed after exposure to nickel sulfate. Compared to rats, mice were more resistant to the development of lung lesions following nickel exposure. In this study, rats were exposed to 0, 0.5, 1, or 2 mg nickel/m^3 as nickel oxide, 0, 0.11, or 0.73 mg nickel/m^3 as nickel subsulf'ide, and 0, 0.03, 0.06, or 0.11 mg nickel/m^3 as nickel sulfate. Mice were exposed to 0, 1, 2, or 3.9 mg nickel/m^3 as nickel oxide, 0, 0.44, or 0.88 mg nickel/m^3 as nickel subsulfide, and 0, 0.06, 0.11, or 0.22 mg nickel/m^3 as nickel sulfate. Lung effects were observed in both rats and mice at all concentrations following exposure to nickel oxide and nickel subsulfide, and at concentrations ≥0.06 mg nickel/m^3 for rats and mice exposed to nickel sulfate. Based on a NOAEL of 0.03 mg nickel/m^3 for rats exposed to nickel sulfate for 2 years (NTP 1996c), a chronic-duration inhalation MRL of $2x10^{-4}$ mg nickel/m^3 for soluble nickel compounds was calculated as described in the footnote to Table 2-l.

2. HEALTH EFFECTS

Cardiovascular Effects. No increases in the numbers of deaths from cardiovascular diseases were reported in workers exposed to nickel (Cornell and Landis 1984; Cox et al. 1981; Cragle et al. 1984).

Microscopic examinations of the hearts of mice and rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 12 6-hour exposures over 16 days did not reveal any changes at concentrations as high as 23.6 mg nickel/m^3 (Benson et al. 1987, 1988; Dunnick et al. 1988). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg nickel/m^3, respectively, or exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, did not result in microscopic changes in the heart (NTP 1996a, 1996b, 1996c). Intermittent exposure (6 hours/day, 5 days/week) of rats to 0.7 mg nickel/m^3 as nickel subsulfide for 78 weeks also did not affect the microscopic appearance of the heart (Ottolenghi et al. 1974).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to nickel.

Microscopic examinations of the gastrointestinal tract of mice and rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 12 6-hour exposures did not reveal any changes at concentrations as high as 23.6 mg nickel/m^3 (Benson et al. 1987, 1988; Dunnick et al. 1988). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg nickel/m^3, respectively, or exposure of mice to nickel oxide, nickel subsulfide or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, did not result in microscopic changes in the gastrointestinal tract (NTP 1996a, 1996b, 1996c). Intermittent exposure of rats to 0.7 mg nickel/m^3 as nickel subsulfide (6 hours/day, 5 days/week) for 78 weeks also did not affect the microscopic appearance of the intestines (Ottolenghi et al. 1974).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to nickel.

A significant reduction in hematocrit was observed in male rats exposed to 0.2 or 0.4 mg nickel/m^3 as nickel oxide 23.6 hours/day for 28 days with no effect in males at 0.8 mg nickel/m^3 (Weischer et al. 1980). A significant increase in hematocrit was observed in female rats exposed to ≥1.6 mg

nickel/m^3 23.6 hours/day for 21 days during pregnancy or at 20.8 mg nickel/m^3 during nonbreeding periods. Male rats were not exposed to the high concentrations of nickel which resulted in increased hematocrits in female rats, and female rats were not exposed to the low concentrations of nickel that resulted in decreased hematocrits in male rats. Therefore, it is not possible to determine if the different hematocrit response in male and female rats exposed to nickel oxide is a gender difference or an exposure concentration difference. Increases in hematocrit values were also noted in rats exposed to nickel subsulfide at 0.73 mg nickel/m^3 for 2 years (NTP 1996b). The investigators did not consider this change to be biologically significant and suggested it may have resulted from mild dehydration. Chronic exposure of rats to nickel oxide or nickel sulfate at concentrations up to 2 or 0.11 mg nickel/m^3, respectively, and chronic exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, did not result in significant hematological effects (NTP 1996a, 1996b, 1996c).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to nickel.

Microscopic examinations of vertebra with spinal cord and femur with bone marrow in mice and rats exposed to nickel sulfate, nickel subsulfide, or nickel oxide for 12 6-hour exposures over 16 days did not reveal any changes at concentrations as high as 23.6 mg nickel/m^3 (Benson et al. 1987, 1988; Dunnick et al. 1988).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to nickel.

Microscopic changes in the liver were not observed in rats or mice exposed to nickel subsulfide, nickel sulfate, or nickel oxide at concentrations of ≤23.6 mg nickel/m3 6 hours/day, 5 days/week, for 16 days (Benson et al. 1988), or ≤ 7.9 mg nickel/m^3 6 hours/day, 5 days/week, for 13 weeks (Benson et al. 1989; Dunnick et al. 1989). Decreased liver weights were observed in rats continuously exposed to nickel sulfate at 0.8 mg nickel/m^3 for 28 days (Weischer et al. 1980). No changes in liver weight were observed at 0.4 mg nickel/m^3. Following chronic exposure, microscopic changes were not observed in the livers of rats exposed to nickel subsulfide at 0.7 mg nickel/m^3 (Ottolenghi et al. 1974) or to nickel oxide at 0.9 mg nickel/m^3 (Tanaka et al. 1988). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to

2, 0.73, or 0.11 mg nickel/m^3, respectively, or exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, did not result in microscopic changes in the liver (NTP 1996a, 1996b, 1996c).

Renal Effects. Marked tubular necrosis was observed in the kidneys of a man who died of adult respiratory distress syndrome 13 days after a go-minute exposure to a very high concentration (382 mg/m^3) of metallic nickel of small particle size (<1.4 μm) (Rendall et al. 1994). Several days after the exposure, urinary concentrations of nickel were 700 μg/L, in comparison to levels of <0.1-13.3 μg/L in persons not occupationally exposed to nickel (Sunderman 1993).

In nickel refinery workers, a significant association was found between nickelemia and increased urinary β_2-microglobulin levels (Sunder-man and Horak 1981). Five of 11 workers with urinary nickel concentrations >l00 μg/L had increased levels of urinary β_2-microglobulin (>240 μg/L). Urinary levels of total proteins, β_2-microglobulin, retinol binding protein, and *N*-acetyl-β-D-glucosaminidase (NAG) were increased in 12 women, and urinary lysozyme and NAG were increased in 14 men occupationally exposed to soluble nickel (sulfate, chloride) compounds at an average concentration of 0.75 mg nickel/m^3 (Vyskocil et al. 1994a). Although the average exposure concentration was the same for women and men, women were more highly exposed as indicated by urine concentrations of 10.3 μg nickel/g creatinine in women compared to 5 μg nickel/g creatinine in men. The markers that were changed reflected tubular dysfunction. No effects on markers of glomerular function, urinary albumin, or transfenin were noted.

A decrease in kidney weight was observed in female rats exposed to ≥0.8 mg nickel/m^3 as nickel oxide 23.6 hours/day during gestation and during a nonbreeding period (Weischer et al. 1980). No changes in kidney weight were observed in male rats exposed to 0.8 mg nickel/m^3 as nickel oxide 23.6 hours/day for 28 days (Weischer et al. 1980). Microscopic changes in the kidneys were not observed in rats or mice exposed to nickel sulfate, nickel subsulfide, or nickel oxide 6 hours/day, 5 days/week, at concentrations of ≤23.6 mg nickel/m^3 for 16 days (Benson et al. 1988), 17.9 mg nickel/m^3 for 13 weeks (Benson et al. 1989; Dunnick et al. 1989), or 0.9 mg nickel/m^3 for 12 months (Tanaka et al. 1988), respectively. Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg nickel/m^3, respectively, and exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9,

0.88, or 0.22 mg nickel/m^3, respectively, did not result in microscopic changes in the kidneys (NTP 1996a, 1996b, 1996c).

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to nickel.

Microscopic examinations did not reveal any changes in the adrenal glands, pancreas, parathyroid, pituitary, or thyroid glands in rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 6-hour exposures over 16 days (Benson et al. 1987, 1988; Dunnick et al. 1988). The maximum concentrations that did not result in deaths or endocrine effects were 13.3, 23.6, and 7.3 mg nickel/m^3 in rats and 0.8, 23.6, and 3.6 mg nickel/m^3 in mice for nickel sulfate, nickel oxide, and nickel subsulfide, respectively. In rats exposed intermittently to nickel subsulfide at 0.7 mg nickel/m3 for 78 weeks, histological changes were not observed in the thyroid or adrenal glands (Ottolenghi et al. 1974). Adrenal medulla hyperplasia was observed in female rats exposed to 2 mg nickel/m^3 as nickel oxide or 0.73 mg nickel/m^3 as nickel subsulfide for 2 years (NTP 1996a, 1996b). This effect was not observed in rats exposed chronically to nickel sulfate at concentrations up to 0.11 mg nickel/m^3, or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations of 3.9, 0.88, or 0.22 mg nickel/m^3, respectively (NTP 1996a, 1996b, 1996c).

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure. However, contact dermatitis in persons exposed to nickel compounds is one of the most common effects of nickel exposure (see Section 2.2.3.2). In addition, immunological studies indicate that the dermatitis is an allergic response to nickel, and significant effects on the immune system have been noted in workers exposed to nickel (see Section 2.2.1.3).

Microscopic changes in the skin were not observed in rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide at concentrations up to 23.6 mg nickel/m^3 for 6 hours/day, 5 days/week, for 16 days (Benson et al. 1987, 1988; Dunnick et al. 1988). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg nickel/m^3, respectively, or exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, did not result in microscopic changes in the skin (NTP 1996a, 1996b, 1996c).

2. HEALTH EFFECTS

Body Weight Effects. Nickel concentrations greater than or equal to those causing respiratory tract effects have been associated with decreased body weight gain in animals. Emaciation was observed in rats exposed to ≥0.8 mg nickel/m^3 as nickel sulfate or nickel subsulfide and in mice exposed to 3.6 mg nickel/m^3 as nickel subsulfide 6 hours/day, 5 days/week, for 16 days (Benson et al. 1987). A 30% decrease in body weight gain was observed in rats exposed to 10.4 mg nickel/m^3 as nickel oxide 23.6 hours/day for 21-28 days (Weischer et al. 1980). In 13-week studies (6 hours/day, 5 days/week), body weights were not affected in rats or mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at 7.9, 1.8, or 0.44 mg nickel/m^3, respectively (Benson et al. 1989; Dunnick et al. 1989; NTP 1996a, 1996b, 1996c). Nickel oxide exposure of rats and mice for 6-months (6 hours/day, 5 days/week) had no effect on body weight at 1.96 mg nickel/m^3 for rats and 3.93 mg nickel/m^3 for mice (Benson et al. 1995a). Decreased body weight (20-30%) was observed in rats exposed intermittently (6 hours/day, 5 days/week) to nickel subsulfide at 0.7 mg nickel/m^3 for 78 weeks (Ottolenghi et al. 1974). Body weights were similar to controls in rats exposed to nickel oxide at 0.7 mg nickel/m^3 7 hours/day, 5 days/week, for 1 year (Tanaka et al. 1988). In a lifetime study (23 hours/day, 7 days/week) in rats exposed to 0.06 mg nickel/m3 as nickel oxide, weight loss began after 13 months of exposure and continued throughout the study (Takenaka et al. 1985). In a 2-year inhalation study, body weights of rats exposed to nickel subsulfide at 0.73 mg nickel/m^3 were ll-12% less than controls during the 2nd year (Dunnick et al. 1995; NTP 1996b). No significant effects on body weight were noted in rats exposed to nickel subsulfide at 0.11 mg nickel/m^3, in rats exposed to nickel sulfate at concentrations up to 0.11 mg nickel/m^3, or in rats exposed to nickel oxide at concentrations up to 2 mg nickel/m^3 for 2 years (Dunnick et al. 1995; NTP 1996a, 1996b, 1996c). In female mice exposed to nickel compounds for 2 years, body weights were 12% lower than controls at 0.22 mg nickel/m^3 as nickel sulfate, and 14% lower than controls at 0.88 mg nickel/m^3 as nickel subsulfide. No significant effects on body weight were noted in mice following exposure to 0.11 mg nickel/m^3 as nickel sulfate, 0.44 mg nickel/m^3 as nickel subsulfide, or 3.9 mg nickel/m^3 as nickel oxide (Dunnick et al. 1995; NTP 1996a, 1996b, 1996c).

Metabolic Effects. No studies were located regarding metabolic effects in humans after inhalation exposure to nickel.

Hypoglycemia was found in female rats following exposure to nickel oxide at 0.8 mg nickel/m^3, 23.6 hours/day, for 21 days, while an increase in serum glucose levels was reported in male rats

following 28 days of exposure to 20.4 mg nickel/m^3 (Weischer et al. 1980). Because male and female rats were not exposed to the same nickel concentrations, it is not possible to determine if the different blood glucose effects in male and female rats is a gender difference or an exposure concentration difference. Although no pancreatic effects have been noted in inhalation studies, a single-dose intravenous injection study has reported effects on serum glucose levels and effects on pancreatic cells in rabbits at doses of 4.5-9 mg nickel/kg as nickel chloride (Kadota and Kurita 1955). It is possible that changes in serum glucose reflect an effect on the pancreas.

2.2.1.3 Immunological and Lymphoreticular Effects

In 38 production workers exposed to nickel (compound not specified), significant increases in levels of immunoglobulin G (IgG), IgA, and IgM and a significant decrease in IgE levels were observed (Bencko et al. 1983, 1986). Significant increases in other serum proteins, that may be involved in cell-mediated immunity (including α_1-antitrypsin, α_2-macroglobulin, ceruloplasmin) were also observed. The increase in immunoglobulins and serum proteins suggests that the immune system was stimulated by nickel exposure. Similar but less-pronounced effects were observed in workers exposed to cobalt. A relationship between nickel and cobalt sensitization is further supported by the finding that nickel-reactive IgE antibodies were observed in eight patients with hard-metal asthma induced by cobalt exposure (Shirakawa et al. 1990). Exposure levels were not reported.

In animals, a decrease in the number of antibody-producing spleen cells was observed in mice exposed for 2 hours to nickel chloride at 0.25 mg nickel/m^3, but not at 0.1 mg nickel/m^3 (Graham et al. 1978). Increased susceptibility to *Streptococci* was observed in mice exposed to 0.46 mg nickel/m^3 as nickel chloride or nickel sulfate for 2 hours (Adkins et al. 1979). Following challenge with Streptococci, the mortality rate was about 20% greater in mice exposed to nickel, compared to controls.

Longer term exposure caused effects on respiratory macrophages (Haley et al. 1990; Morimoto et al. 1995; Spiegelberg et al. 1984). An increase in the production of tumor necrosis factor by alveolar macrophages was observed in rats exposed to nickel oxide at 9.2 mg/m^3, 8 hours/day, 5 days/week, for 4 weeks (Morimoto et al. 1995). A decrease in alveolar macrophage phagocytic activity was observed in mice exposed to ≥0.45 mg nickel/m^3 as nickel subsulfide, nickel sulfate, or nickel oxide, 6 hours/day, 5 days/week, for 65 days (Haley et al. 1990). Mice exposed to nickel

sulfate showed decreased resistance to tumor challenge. Decreases in the number of alveolar macrophages and in the humoral response (as indicated by decreased antibody synthesis against injected sheep erythrocytes) were observed in rats after 14 months of continuous exposure to 0.025 mg nickel/m^3 as nickel oxide, indicating that inhalation exposure to nickel may make animals more susceptible to infection (Spiegelberg et al. 1984). The increase in susceptibility was also exhibited by rabbits exposed to 1.0 mg nickel/m^3 as metallic nickel 6 hours/day, 5 days/week, for 3-6 months (Johansson et al. 1981). All of the animals exposed for 6 months had foci of pneumonia, which may have resulted from an impaired function of the alveolar macrophages.

Atrophy of lymphoid organs (spleen and thymus) and lymphoid hyperplasia in bronchial and mediastinal lymph nodes were observed in rats and mice exposed 6 hours/day for 12 of 16 days to 21.6 mg nickel/m^3 as nickel sulfate, ≥3.6 mg nickel/m^3 as nickel subsulfide, and 23.6 mg nickel/m^3 as nickel oxide (Benson et al. 1987, 1988; Dunnick et al. 1988). The atrophy of the lymphoid organs was considered secondary to the decrease in body weight (Benson et al. 1987, 1988; Dunnick et al. 1988). According to the series of 16-day and 13-week studies by Haley et al. (1990), Benson et al. (1987, 1988, 1989), and Dunnick et al. (1988, 1989), nickel toxicity is ranked as follows: nickel sulfate > nickel subsulfide > nickel oxide. The lowest concentration of nickel sulfate resulting in mild lymphoid hyperplasia in the 13-week studies was 0.22 mg nickel/m^3 in rats and 0.44 mg nickel/m^3 in mice (Dunnick et al. 1989; NTP 1996c). Following chronic exposure, bronchial lymph node hyperplasia was observed in rats exposed to 0.5 mg nickel/m^3 as nickel oxide, 0.11 mg nickel/m^3 as nickel subsulfide, and 0.11 mg nickel/m^3 as nickel sulfate, and in mice exposed to 1 mg nickel/m^3 as nickel oxide, 0.44 mg nickel/m^3 as nickel subsulfide, and 0.22 mg nickel/m^3 as nickel sulfate (NTP 1996a, 1996b, 1996c).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects for each species, duration category, and nickel compound are recorded in Table 2-l and plotted Figure 2-l.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to nickel.

Microscopic examinations did not reveal any changes in the brains of rats or mice exposed to nickel as nickel sulfate, nickel oxide, or nickel subsulfide for 12 6-hour exposures over 16 days (Benson et al. 1987, 1988; Dunnick et al. 1988). The maximum concentrations that did not result in deaths or changes in brain histology were 13.3, 23.6, and 7.3 mg nickel/m^3 in rats for nickel sulfate, nickel oxide, and nickel subsulfide, respectively, and 0.8, 23.6, and 3.6 mg/m^3 in mice for nickel sulfate, nickel oxide, and nickel subsulfide, respectively. In rats exposed intermittently (6 hours/day, 5 days/week) to nickel subsulfide at 0.7 mg nickel/m^3 for 78 weeks, histological changes were not observed in the brain (Ottolenghi et al. 1974). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg nickel/m^3, respectively, or exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, did not result in microscopic changes in the brain (NTP 1996a, 1996b, 1996c).

As noted in Section 2.2.1.2, atrophy of the olfactory epithelium has been observed in rats exposed to nickel sulfate and nickel subsulfide (Benson et al. 1987, 1988, 1989; Dunnick et al. 1988, 1989). To determine if changes in the olfactory epithelium result in any functional changes, Evans et al. (1995) completed behavioral studies of olfactory absolute threshold and olfactory discrimination in rats exposed to nickel sulfate at 0.635 mg/m^3 6 hours/day for 16 days. Although histological changes were observed in the olfactory epithelium, no functional changes were noted. Camosine, a neurochemical marker, was reduced in the olfactory epithelium following 12 days of exposure but was back to control levels by exposure day 16, suggesting adaption to nickel exposure.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species, duration category, and nickel compound are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.1.5 Reproductive Effects

Compared to 352 local female construction workers in which the spontaneous abortion rate was 8.5%, an increase in spontaneous abortions to 15.9% was observed among 356 women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). Exposure concentrations were 0.084.196 mg nickel/m^3, primarily as nickel sulfate, and nickel concentrations in the urine were 3.2-22.6 µg/L. Nickel levels in the urine of persons not

occupationally exposed are generally <0.1-13.3 μg/L (Sunderman 1993). The investigators noted that the nickel-exposed women manually lifted heavy nickel anodes and that they may have experienced heat stress.

Testicular degeneration was observed in rats and mice exposed to nickel sulfate (≥1.6 mg nickel/m^3) and nickel subsulfide (≥1.8 mg nickel/m^3 for rats and ≥3.6 mg nickel/m^3 for mice) 6 hours/day for 12 days over a 16-day period (Benson et al. 1987, 1988). The study authors indicated that testicular lesions were probably the result of emaciation rather than a direct effect of nickel (Benson et al. 1987). That testicular effects are secondary to generalized emaciation is supported by intermediate-duration studies. At doses that did not cause emaciation, no exposure-related effects were seen in sperm motility, or morphology. Sperm numbers were decreased by 21% in rats exposed to nickel oxide at 7.9 mg nickel/m^3, with no effects at 3.9 mg/m^3. No effects on sperm numbers were observed in rats exposed to nickel subsulfide or nickel sulfate at concentrations up to 1.8 and 0.44 mg nickel/m^3, respectively, or in mice exposed to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 7.9, 1.8, or 0.44 mg nickel/m^3, respectively (Dunnick et al. 1989; NTP 1996a, 1996b, 1996c). Histological changes in the testes were not observed. No effect on the length of the estrous cycle was noted in mice or rats exposed to nickel sulfate at ≤0.44 mg nickel/m^3, nickel oxide at ≤7.9 mg nickel/m^3, or nickel subsulfide at ≤1.8 mg nickel/m^3 6 hours/day, 5 days/week, for 13 weeks (Dunnick et al. 1989; NTP 1996a, 1996b, 1996c). Chronic exposure of rats to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 2, 0.73, or 0.11 mg nickel/m^3, respectively, and exposure of mice to nickel oxide, nickel subsulfide, or nickel sulfate at concentrations up to 3.9, 0.88, or 0.22 mg nickel/m^3, respectively, did not result in microscopic changes in the reproductive organs (NTP 1996a, 1996b, 1996c). These acute-, intermediate-, and chronic-duration studies do not clearly identify a LOAEL for reproductive effects following inhalation exposure to nickel and suggest that relative to the respiratory tract, nickel is not a reproductive toxicant following inhalation exposure.

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species, duration category, and nickel compound are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.1.6 Developmental Effects

Compared to 342 local female construction workers in which the structural malformation rate was 5.8%, an increase in structural malformations to 16.9% was observed among 356 women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). Although the investigators indicate that the difference was statistically significant, a p value was not provided, and the statistical test used was not stated. Although the specific structural malformations found were not stated, the investigators state that relative risks were 2.9 for all kinds of defects, 6.1 for cardiovascular system defects, and 1.9 for musculoskeletal defects. Exposure concentrations were 0.08-0.196 mg nickel/m^3, primarily as nickel sulfate, and nickel concentrations in the urine were 3.2-22.6 μg/L. Nickel levels in the urine of persons not occupationally exposed are generally <0.1-13.3 μg/L (Sunderman 1993). The investigators noted that the nickel-exposed women manually lifted heavy nickel anodes and that they may have experienced heat stress.

A decrease in fetal body weight was observed in the offspring of rats exposed to 1.6 mg nickel/m^3 as nickel oxide 23.6 hours/day on gestation days 1-21 (Weischer et al. 1980). No effect on fetal body weight was observed at 0.8 mg nickel/m^3, although decreased maternal body weight gain was observed at this concentration. No effects on the number of fetuses or on the weight of placentae were observed.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species. duration category, and nickel compound are recorded in Table 2-l and plotted Figure 2-l.

2.2.1.7 Genotoxic Effects

A significant increase in the incidence of chromosomal aberrations (gaps) was observed in the lymphocytes of 11 nickel workers exposed to nickel monosulfide and nickel subsulfide (mean concentrations of 0.2 or 0.5 mg nickel/m^3, respectively) (Waksvik and Boysen 1982). No significant increase in the incidence of chromosomal breaks or sister chromatid exchanges was observed. No relationships were found among the incidence of chromosomal gaps and plasma nickel concentration, duration of exposure, or age of the workers (Waksvik and Boysen 1982). A slight but significant increase in the incidence of chromosomal aberrations was observed in

lymphocytes of 55 welders exposed to iron, manganese, and nickel (Elias et al. 1989). A significant correlation was found between the length of employment (10-24 years) and the incidence of chromosomai aberrations. No correlation was found, however, between nickel exposure levels and the incidence of aberrations. Nickel could not be identified as the sole causal agent because the workers were exposed to other chemicals such as manganese.

No studies were located regarding genotoxic effects in animals after inhalation exposure to nickel.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Epidemiology studies of workers exposed to nickel have demonstrated a carcinogenic effect. Most studies of nickel-exposed workers are confounded, however, because exposure is to impure nickel compounds that often contain relatively high concentrations of other metals, including arsenic, which is also a carcinogen. Many nickel-exposed workers are also exposed to irritant gases including hydrogen sulfide, ammonia, chlorine, and sulfur dioxide (IARC 1990). Lung and nasal cancer were the forms of cancer in the nickel-exposed workers (Chovil et al. 1981; Doll et al. 1977; Enterline and Marsh 1982; Magnus et al. 1982). The workers were primarily exposed to nickel refinery dust (Chovil et al. 1981; Doll et al. 1977). In one cohort of 1,916 refinery workers, the ratio of observed to expected deaths was 7:l for lung cancer and 40:l for nasal cancer (Pedersen et al. 1973). In an analysis of 100 cases of nasal cancers in male nickel refinery workers, the cancers were primarily squamous cell carcinomas (48%), anaplastic and undifferentiated carcinomas (39%), and adenocarcinomas (6%) (Sunderman et al. 1989a). This distribution was comparable to that found in the general population. Higher concentrations of nickel were found in the nasal mucosa of active and retired workers compared to unexposed controls, and the nickel was cleared from the nasal mucosa with an estimated half-life of 3.5 years (Torjussen 1985; Tojussen and Andersen 1979). In an analysis of 259 cases of lung cancer in nickel refinery workers, the cancers were primarily squamous cell carcinomas (67%), anaplastic, small cell, and oat cell carcinomas (15%), and adenocarcinomas (8%) (Sunderman et al. 1989a). Compared to the general population, the workers had a greater incidence of squamous cell carcinomas and fewer adenocarcinomas. In the general population, lung cancer in women is more likely to be adenocarcinoma. Therefore, rather than indicating nickel-specific tumor types, these data may reflect the lack of women in the cohort

of nickel workers and temporal trends over the 60 years during which the tumors were diagnosed (Sunderman et al. 1989a). The number of refinery workers with lung cancer that were women was not stated.

The latency period for the lung cancer has been found to be shorter than for nasal cancer. In a cohort of 2,247 refinery workers, an excess of lung cancer was found by 3-14 years after first employment, while an increase in nasal cancer was not found until 15-24 years after first employment (Magnus et al. 1982). The risk of respiratory tract cancers markedly decreased when the date of first exposure was later than ≈1930 (Doll et al. 1970, 1977; Pedersen et al. 1973). This was a result of reducing nickel dust exposure by altering the machinery used in the refining process and by the use of cotton face pads by the workers (Doll et al. 1977). The interaction between smoking and nickel exposure for the development of respiratory tract cancer was found to be additive rather than multiplicative (Magnus et al. 1982).

In a population of sinter plant workers, the risk of death from cancer of the lung or nose has not been shown to decrease even 30-40 years after the workers left the sinter plant (Muir et al. 1994). Although the workers left the sintering operation, many were still exposed to nickel compounds, in operations that have not been associated with cancer. The investigators note that persisting nickel deposits could act as carcinogenic agents.

An increase in the incidence of respiratory cancer has not been observed in males living in New Caledonia, where about a quarter of the male population aged 25-70 either works or has worked in nickel mining or refining (Goldberg et al. 1994). The investigators suggested that the reason for the lack of an effect was that these workers were exposed to lower concentrations of nickel (<2 mg/m^3) than other refinery workers, and the nickel was primarily in the form of nickel silicate oxide ore and oxidic nickel.

In a reanalysis of most of the epidemiology studies of nickel workers (discussed in the previous paragraphs), it was found that lung and nasal cancers were related primarily to exposure to lesssoluble compounds at concentrations of ≥10 mg nickel/m^3 (primarily oxidic and sulfidic compounds) (International Committee on Nickel Carcinogenesis in Man 1990). A higher incidence of lung and nasal cancer was observed among workers exposed to both soluble and less-soluble nickel compounds, compared to those exposed to less-soluble nickel compounds alone, indicating an effect

of soluble nickel, or an interaction between soluble and less-soluble nickel compounds. The effect of soluble nickel compounds was observed at concentrations of >l mg nickel/m^3. No evidence was found that metallic nickel causes respiratory cancer. After reanalysis of all the data, the International Committee on Nickel Carcinogenesis in Man (1990) concluded that inhalation exposure to nickel compounds was not associated with cancers other than those of the lungs and nasal cavity.

Nickel refinery dust and nickel subsulfide have been classified by EPA as class A human carcinogens (IRIS 1996). Other nickel compounds have not been classified by the EPA. The Department of Health and Human Services (DHHS 1994) has determined that nickel may reasonably be anticipated to be a carcinogen. The concentration of 10 mg nickel/m^3 as less-soluble nickel compounds is presented as a human Cancer Effect Level for lung and nasal cancers in Table 2-l and Figure 2-l. Based on the occupational data, a slope factor of $4.8x10^{-4}$ ($\mu g/m^3$) for the inhalation of nickel refinery dust, which was believed to have been nickel subsulfide, was derived (IRIS 1996). The risk levels range from $4x10^{-1}$ to $4x10^{-4}$ $\mu g/m^3$ for a risk ranging from $1x10^{-4}$ to $1x10^{-7}$, respectively, for nickel refinery dust (IRIS 1996). These risk levels are presented in Figure 2-l.

Acute (6 hours/day, 5 days/week, for 1 month) inhalation exposure to ≤6.3 mg nickel/m^3 as nickel oxide resulted in no significant increase in lung cancer in rats 120 months after exposure (Horie et al. 1985). Chronic (6 hours/day, 5 days/week, for 78 weeks) exposure to nickel subsulfide, however, resulted in an increase in lung tumors in rats exposed to 0.7 mg nickel/m^3 (Ottolenghi et al. 1974). The tumors included adenomas, adenocarcinomas, squamous cell carcinomas, and fibrosarcoma. No increase in lung tumors was observed in mice following weekly intratracheal injections of ≤0.8 mg nickel/m^3 as nickel subsulfide for ≤15 weeks, followed by observation for ≤27 months (Fisher et al. 1986; McNeil1 et al. 1990). Tumor incidence may not have increased because of efficient clearance of nickel from the lungs and early repair of lung lesions following intratracheal administration (Fisher et al. 1986).

Two-year inhalation carcinogenicity bioassays have shown nickel oxide and nickel subsulfide to be carcinogenic in rats resulting in alveolar/bronchiolar adenomas and carcinomas, and benign and malignant pheochromocytomas of the adrenal medulla (Dunnick et al. 1995; NTP 1996a, 1996b). In mice, there was no evidence of a carcinogenic effect of nickel subsulfide in either sex, no evidence of a carcinogenic effect of nickel oxide in males, and equivocal evidence of carcinogenic

activity of nickel oxide in females based on observations of alveolarbronchiolar adenomas and carcinomas. Nickel sulfate was not carcinogenic in either rats or mice (Dunnick et al. 1995; NTP 1996c). The tumor incidences and the exposure concentrations used in these studies are shown in Table 2-2 for rats and Table 2-3 for mice. The nickel concentrations as nickel subsulfide and nickel oxide resulting in cancer in rats are presented as Cancer Effect Levels in Table 2-l and Figure 2- 1.

2.2.2 Oral Exposure

2.2.2.1 Death

One human death following oral exposure to nickel was reported (Daldrup et al. 1983). Nickel sulfate crystals (rough estimate of 570 mg nickel/kg) were accidentally ingested by a 2-year-old child. Four hours after ingestion, cardiac arrest occurred, and the child died 8 hours after exposure.

Single-dose oral lethality studies indicate that soluble nickel compounds are more toxic than less soluble nickel compounds. Oral LD_{50} values of 39 mg nickel/kg as nickel sulfate in female rats (Mastromatteo 1986) and 116 and 136 mg nickel/kg as nickel acetate in female rats and male mice (Haro et al. 1968) have been reported for soluble nickel compounds. In contrast, the oral LD_{50}s in rats for less-soluble nickel oxide and subsulfide were >3,930 and >3,665 mg nickel/kg, respectively (Mastromatteo 1986).

Rats died after gavage treatment for 91 days with 8.6 (6/52) or 1.2 (2/60) mg nickel/kg/day as nickel chloride hexahydrate (American Biogenics Corporation 1988). Clinical signs observed included lethargy, ataxia, irregular breathing, hypothermia, salivation, squinting, and loose stools. As part of a longer term study, rats were provided with drinking water containing 1,000 ppm nickel as nickel chloride (approximately 140 mg/kg/day) (RTI 1988a). Within 2 weeks, 7/62 died and the dose was eliminated from the study. In other studies, all rats provided with nickel chloride in the drinking water at doses up to 92 mg nickel/kg for 15 days survived (RTI 1985), and all mice provided with nickel sulfate in the drinking water at doses up to 150 mg nickel/kg/day for 180 days survived (Dieter et al. 1988).

TABLE 2-2. Alveolar/Bronchiolar Neoplasms and Adrenal Medulla Proliferative Lesions in Rats[a]

	Number of rats with neoplasms or proliferative lesions/number of rats examined										
	Exposure to nickel sulfate hexahydrate (mg nickel/m^3)				Exposure to nickel subsulfide (mg nickel/m^3)			Exposure to nickel oxide (mg nickel/m^3)			
Effect	0	0.03	0.06	0.11	0	0.11	0.73	0	0.5	1	2
Male											
Alveolar/ bronchiolar adenoma/ carcinoma	2/54	0/53	1/53	3/53	0/53	6/53[b]	11/53[c]	1/54	1/53	6/53[d]	4/52[d]
Adrenal medulla benign or malignant pheochromo-cytoma	16/54	19/55	13/55	12/55	14/53	30/53[c]	42/53[c]	27/54	24/53	27/53	35/54[c]
Female											
Alveolar/ bronchiolar adenoma/ carcinoma	0/52	0/53	0/53	1/54	2/53	6/53[d]	9/53[b]	1/53	1/53	6/53[d]	5/54[d]
Adrenal medulla benign or malignant pheochromo-cytoma	2/52	4/53	2/53	3/54	3/53	7/53	36/53[c]	4/53	7/53	6/53	18/54[c]

[a]modified from Dunnick et al. 1995
[b]$p \leq 0.05$
[c]$p \leq 0.01$
[d]$p \leq 0.05$ versus historical data (1.4%, 3/210 males; 1.4%, 4/208 females)

TABLE 2-3. Alveolar/Bronchiolar Neoplasms in Mice[a]

	Number of mice with tumors/number of mice examined										
	Exposure to nickel sulfate hexahydrate (mg nickel/m^3)				Exposure to nickel subsulfide (mg nickel/m^3)			Exposure to nickel oxide (mg nickel/m^3)			
Gender	0	0.06	0.11	0.22	0	0.44	0.88	0	1	2	3.9
Male	13/61	18/61	7/62	8/61	13/61	5/59	6/58	9/57	14/67	15/66	14/69
Female	7/61	6/60	10/60	1/60	9/58	2/59	3/60	6/64	15/66[b]	12/63	8/64

[a]Modified from Dunnick et al. 1995
[b]$p \leq 0.05$

In a multigeneration study (RTI 1988a, 1988b) in which rats were treated with nickel chloride in the drinking water, the death of female rats from pregnancy complications at the time of delivery suggests that females are more susceptible to nickel toxicity during parturition. Although the number of deaths was not significantly above controls and not clearly dose related (P_0: 0/31 in controls, l/31 at 7 mg/kg/day, 3/30 at 31 mg/kg/day, and 3/31 at 53 mg/kg/day; F_1: 0/30 at 0 and 8 mg/kg/day, 3/30 at 28 mg/kg/day, and l/30 at 50 mg/kg/day), death in dams during delivery is a relatively rare event. The results of this study (RTI 1988a, 1988b) are confounded by a decrease in food and water intake observed in the exposed animals. Deaths in offspring before weaning have also been reported in multigeneration, multilitter studies (RTI 1988a, 1988b; Schroeder and Mitchener 1971; Smith et al. 1993). Because cross-fostering studies have not been completed, it is not possible to know if the pre-weaning deaths are a result of an inherent defect in the pups, nickel exposure through the milk, or a change in the quality or quantity of the milk produced by the dam (Smith et al. 1993).

An increase in mortality was not observed in chronic studies in rats or dogs fed nickel sulfate in the diet at doses up to 188 mg/kg/day for rats and 62.5 mg/kg/day for dogs (Ambrose et al. 1976). In mice provided with 0.95 mg/nickel/kg as nickel acetate in drinking water for up to 904 days, an increase in life expectancy was observed (Schroeder and Mitchener 1975).

Oral LD_{50} values and all LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects for each species, duration category, and nickel compound are recorded in Table 2-4 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to nickel.

Pneumonitis was observed in 6/19 male rats and 9117 female rats treated for 91 days by gavage with 8.6 mg nickeUkg/day as nickel chloride (American Biogenics Corporation 1988). In a

multigeneration study (RTI 1988a, 1988b), increased lung weights were observed in rats provided with nickel chloride in the drinking water at 53 mg nickel/kg/day, and an increase in cellular

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral

Key to figure[a]	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)	LOAEL (effect) Serious (mg Ni/kg/day)	Reference/ Chemical form
	ACUTE EXPOSURE						
	Death						
1	Human	once				570 F (death)	Daldrup et al. 1983 sulfate
2	Rat (Fischer- 344)	once (G)				116 F (LD_{50}) 120 M (LD_{50})	Haro et al. 1968 acetate
3	Rat (Sprague-Dawley)	once (G)				39 F (LD_{50}) 46 M (LD_{50})	Mastromatteo 1986 sulfate
4	Mouse (Swiss-Webster)	once (G)				136 M (LD_{50}) 139 F (LD_{50})	Haro et al. 1968 acetate
	Systemic						
5	Human	2 d 2x/d (C)	Derm		0.03 (allergic dermatitis)		Burrows et al. 1981 sulfate
6	Human	once (C)	Derm		0.01 F (allergic dermatitis)		Cronin et al. 1980 sulfate
7	Human	once or 1 dose for 2 d (C)	Derm	0.043 F	0.097 F (allergic dermatitis)		Gawkrodger et al. 1986 sulfate

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)	LOAEL (effect) Serious (mg Ni/kg/day)	Reference/ Chemical form
8	Human	1 d (W)	Gastro			7.1 M (vomiting, cramps, diarrhea)	Sunderman et al. 1988 sulfide/chloride
			Hemato		7.1 M (increased reticulocytes)		
			Musc/skel		7.1 M (muscular pain)		
			Hepatic		7.1 M (increased serum bilirubin)		
			Renal		7.1 M (increased urine albumin)		
	Neurological						
9	Human	1 d (W)			7.1 M (giddiness, headache, weariness)		Sunderman et al. 1988 sulfate/chloride
10	Human	once (W)		0.018		0.05 (transient impaired vision, single case)	Sunderman et al. 1989b sulfate
	Reproductive						
11	Mouse (lacca)	once (GW)			23M (3.7-fold increase in sperm head abnormalities)		Sobti and Gill 1989 nitrate
	Developmental						
12	Mouse	Gd 8-12 (GW)		90.6			Seidenberg et al. 1986 chloride

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)	LOAEL (effect) Serious (mg Ni/kg/day)	Reference/ Chemical form
	INTERMEDIATE EXPOSURE						
	Death						
13	Rat (Sprague-Dawley)	91 d daily (GW)				1.2 (2/60 died)	American Biogenics Corp 1988 chloride
14	Rat (CD)	F: 30 wk M: 24 wk (W)				7 F (1/31 pregnant rats died)	RTI 1988a chloride
	Systemic						
15	Human	91-178 d (W)	Derm	0.02 F			Santucci et al. 1994 sulfate
16	Rat (Sprague-Dawley)	91 d daily (GW)	Resp			8.6 (pneumonitis)	American Biogenics Corp 1988 chloride
			Cardio	1.2	8.6 (decreased heart weight)		
			Gastro	8.6			
			Hemato	1.2	8.6 (increased white blood cell counts)		
			Hepatic	1.2	8.6 M (decreased liver weight)		
			Renal	1.2	8.6 F (decreased kidney weight)		
			Derm	8.6			
			Ocular	8.6			
			Bd Wt	1.2		8.6 M (26% decrease in body weight gain)	

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)	LOAEL (effect) Serious (mg Ni/kg/day)	Reference/ Chemical form
17	Rat (CD)	F: 30 wk M: 24 wk (W)	Resp	31 F	53 F (increased lung weight)		RTI 1988a chloride
			Cardio	53 F			
			Hepatic	53 F			
			Renal	53 F			
			Endocr	4 M	20M (increased pituitary weight)		
			Bd Wt	31 F	53 F (body weight 11% lower than controls)		
18	Rat (CD)	M: 21-24 wk F: 27-30 wk (W)	Resp	4 M	20M (histiocytic cellular infiltration of the lungs)		RTI 1988b chloride
			Hepatic	28 F	50 F (decreased liver weight)		
			Renal	28 F	50 F (increased kidney weight)		
			Endocr	4 M	20M (increased pituitary weight)		
19	Rat (Long- Evans)	11 wk breeding-lactation 2 litters (W)	Endocr	6.8 F	31.6 F (21% decreased prolactin)		Smith et al. 1993 chloride
			Bd Wt	31.6 F			
20	Rat (Wistar)	3 or 6 mo (W)	Renal		7.6 F (significantly increased urinary albumin)		Vyskocil et al. 1994b sulfate
			Bd Wt	7.6 F			

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)	LOAEL (effect) Serious (mg Ni/kg/day)	Reference/ Chemical form
21	Rat (Wistar)	28 d (W)	Hemato	0.38 M	0.75 M (increased leukocytes)		Weischer et al. 1980 chloride
			Hepatic	0.75 M	1.5 M (decreased liver weight)		
			Renal	0.75 M	1.5 M (decreased kidney weight)		
			Bd Wt			0.38 M (20% decreased body weight gain)	
22	Rat (OSU brown)	6 wk (F)	Hemato	5 M	25 M (10% decreased hemoglobin)		Whanger 1973 acetate
			Bd Wt	5 M		25 M (88% decrease in body weight gain)	
23	Mouse (B6C3F1)	180 d daily (W)	Hepatic	108 F	150 F (decreased liver weight)		Dieter et al. 1988 sulfate
			Renal	44 F	108 F (minimal convoluted tubular damage)		
			Bd Wt	44 F	108 F (body weight 10% lower than controls)	150 F (body weight 26% lower than controls)	
	Immuno/Lymphor						
24	Mouse (B6C3F1)	180 d daily (W)			44 F (decrease in relative thymus weight)	108 F (decrease in bone marrow cellularity)	Dieter et al. 1988 sulfate
25	Mouse (BALB/c)	10-11wk (W)			20.3 F (enhanced inflammatory response in the hearts of mice challenged with coxsackie virus B3)		Ilback et al. 1994 chloride

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)	LOAEL (effect) Serious (mg Ni/kg/day)		Reference/ Chemical form
	Neurological							
26	Rat (Sprague-Dawley)	91 d daily (GW)		1.2		8.6	(ataxia, prostation, hypothermia)	American Biogenics Corp 1988 chloride
	Reproductive							
27	Rat (Wistar)	about 24 wk (F)				22.5	(increase in the number of stillborn pups in the first generation)	Ambrose et al. 1976 sulfate
28	Rat (Long- Evans)	11 wk breeding-lactation 2 litters (W)				1.3	(9-11% of pups died)	Smith et al. 1993 chloride
29	Mouse (CD-1)	Gd 2-17 (W)		80		160	(spontaneous abortions)	Berman and Rehnberg 1983 chloride
	Developmental							
30	Rat (CD)	M: 24 wk F: 30 wk (W)		31		53	(reduced pup body weights)	RTI 1988a chloride

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)		LOAEL (effect) Serious (mg Ni/kg/day)		Reference/ Chemical form
	CHRONIC EXPOSURE								
	Systemic								
31	Rat (Wistar)	2 yrs (F)	Resp	187.5					Ambrose et al. 1976 sulfate
			Cardio	187.5					
			Gastro	187.5					
			Hemato	187.5					
			Musc/skel	187.5					
			Hepatic	7.5 F	75 F	(decreased liver weights)			
			Renal	187.5					
			Endocr	187.5					
			Derm	187.5					
			Bd Wt	7.5	75	(10-18% decreased body weight gain)	187.5	(27-29% decreased body weight gain)	

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)		LOAEL (effect) Serious (mg Ni/kg/day)		Reference/ Chemical form
32	Dog (Beagle)	2 yrs (F)	Resp	25			62.5	(cholesterol granulomas, emphysema, bronchiolectasis)	Ambrose et al. 1976 sulfate
			Cardio	62.5					
			Gastro	25	62.5	(vomiting that stopped after doses were lowered and incrementally increased to 62.5 at 2 week intervals)			
			Hemato	25	62.5	(low hematocrit)			
			Musc/skel	62.5					
			Hepatic	25	62.5	(increased liver weight)			
			Renal	62.5					
			Endocr	62.5					
			Derm	62.5					
			Bd Wt	25	62.5	(10% decrease in body weight gain)			
	Immuno/Lymphor								
33	Rat (Wistar)	2 yrs (F)		187.5					Ambrose et al. 1976 sulfate
34	Dog (Beagle)	2 yrs (F)		62.5					Ambrose et al. 1976 sulfate
	Neurological								
35	Rat (Wistar)	2 yrs (F)		187.5					Ambrose et al. 1976 sulfate

TABLE 2-4. Levels of Significant Exposure to Nickel - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg Ni/kg/day)	LOAEL (effect) Less serious (mg Ni/kg/day)	LOAEL (effect) Serious (mg Ni/kg/day)	Reference/ Chemical form
36	Dog (Beagle)	2 yrs (F)		62.5			Ambrose et al. 1976 sulfate

[a]The numbers correspond to entries in Figure 2-2. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Derm = dermal; Endocr = endocrine; F = female; (F) = food; (G) = gavage - not specificed; Gastro = gastrointestinal; Gd = gestation day; (GW) = gavage - water; Hemato = hematological; Immuno/Lymphor = immunological lymphoreticular; LD50 = lethal dose 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); Musc/skel =musculoskeletal; Ni = nickel; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yrs = years

Figure 2-2. Levels of Significant Exposure to Nickel – Oral

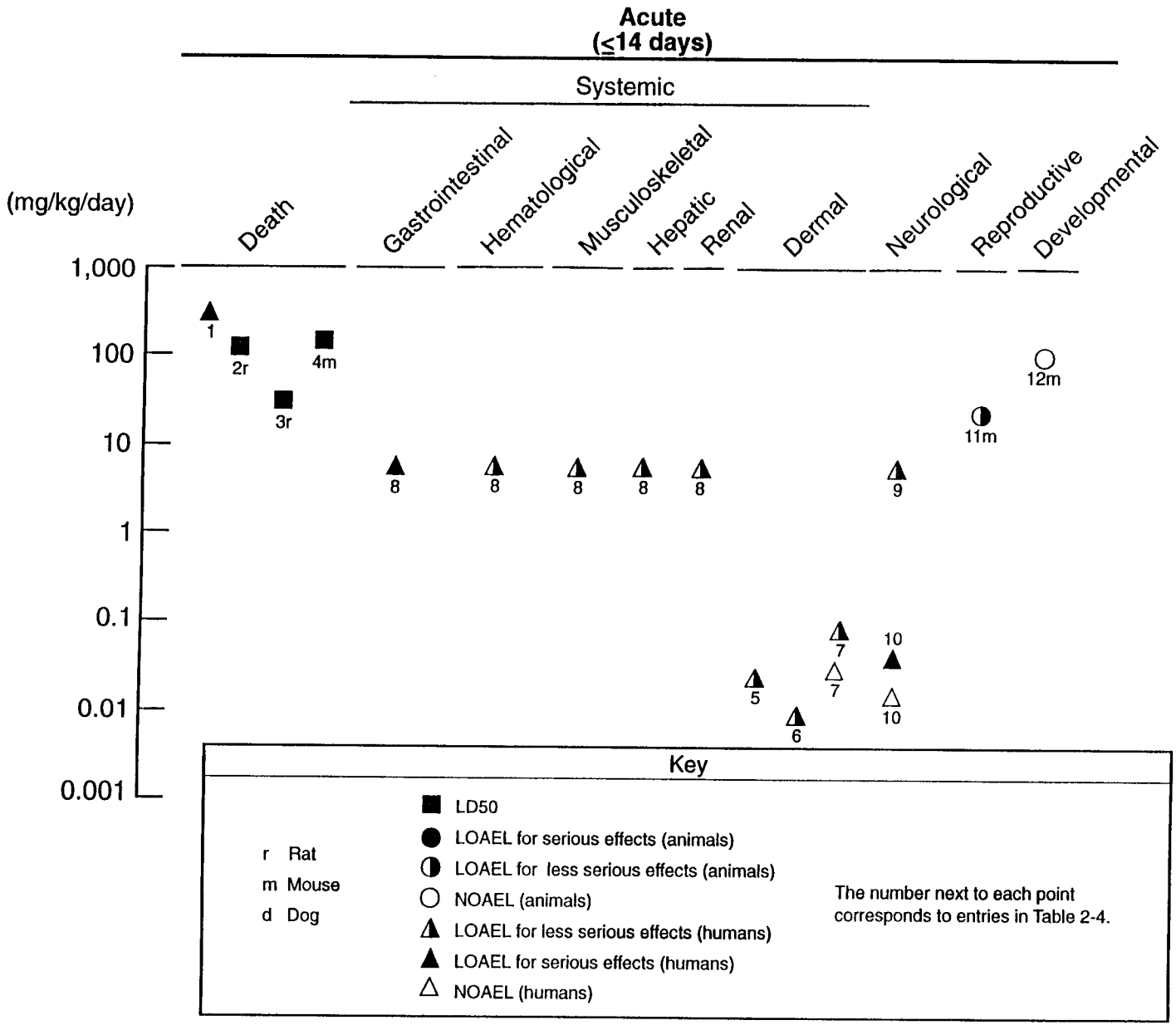


Figure 2-2. Levels of Significant Exposure to Nickel – Oral (continued)

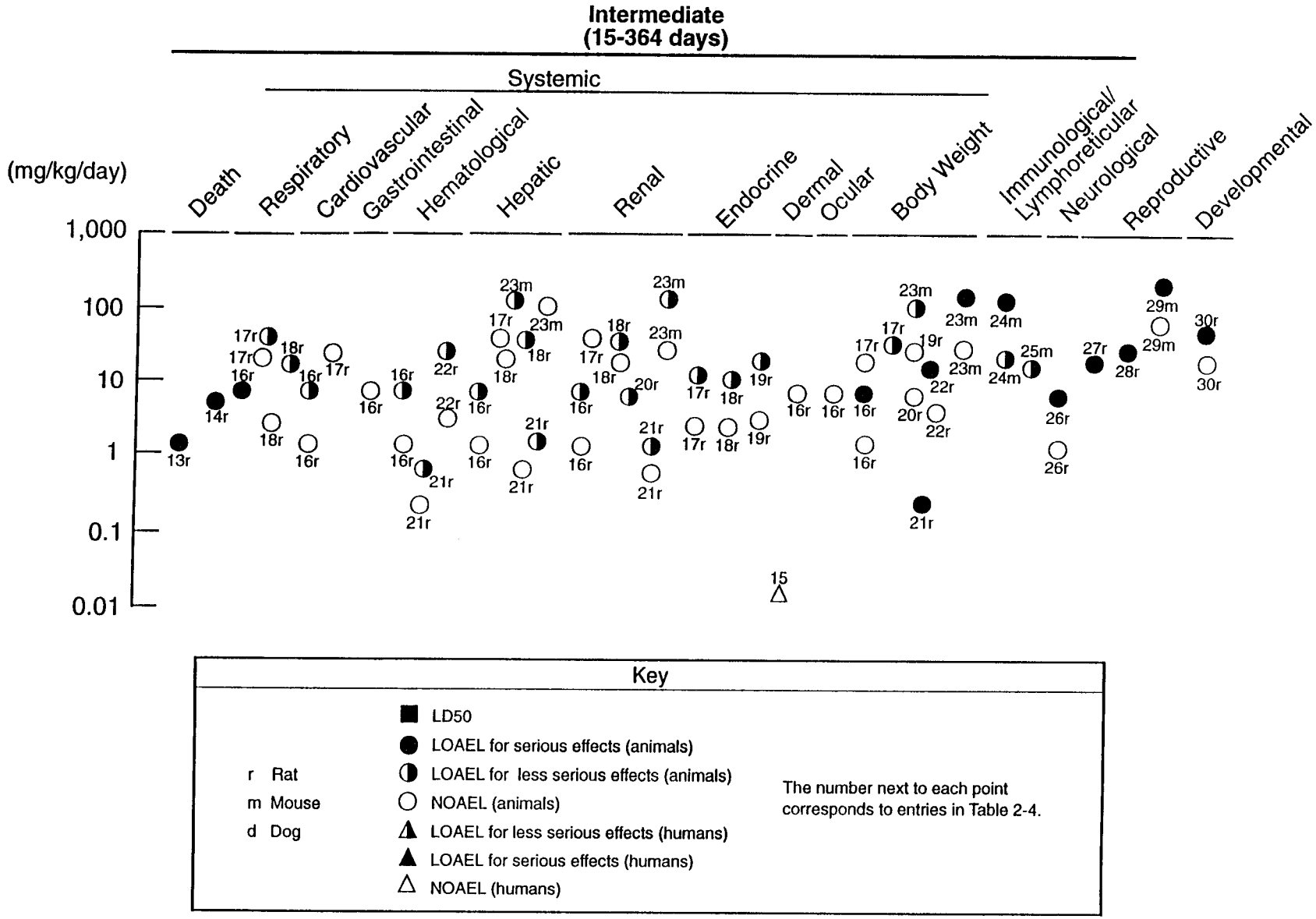
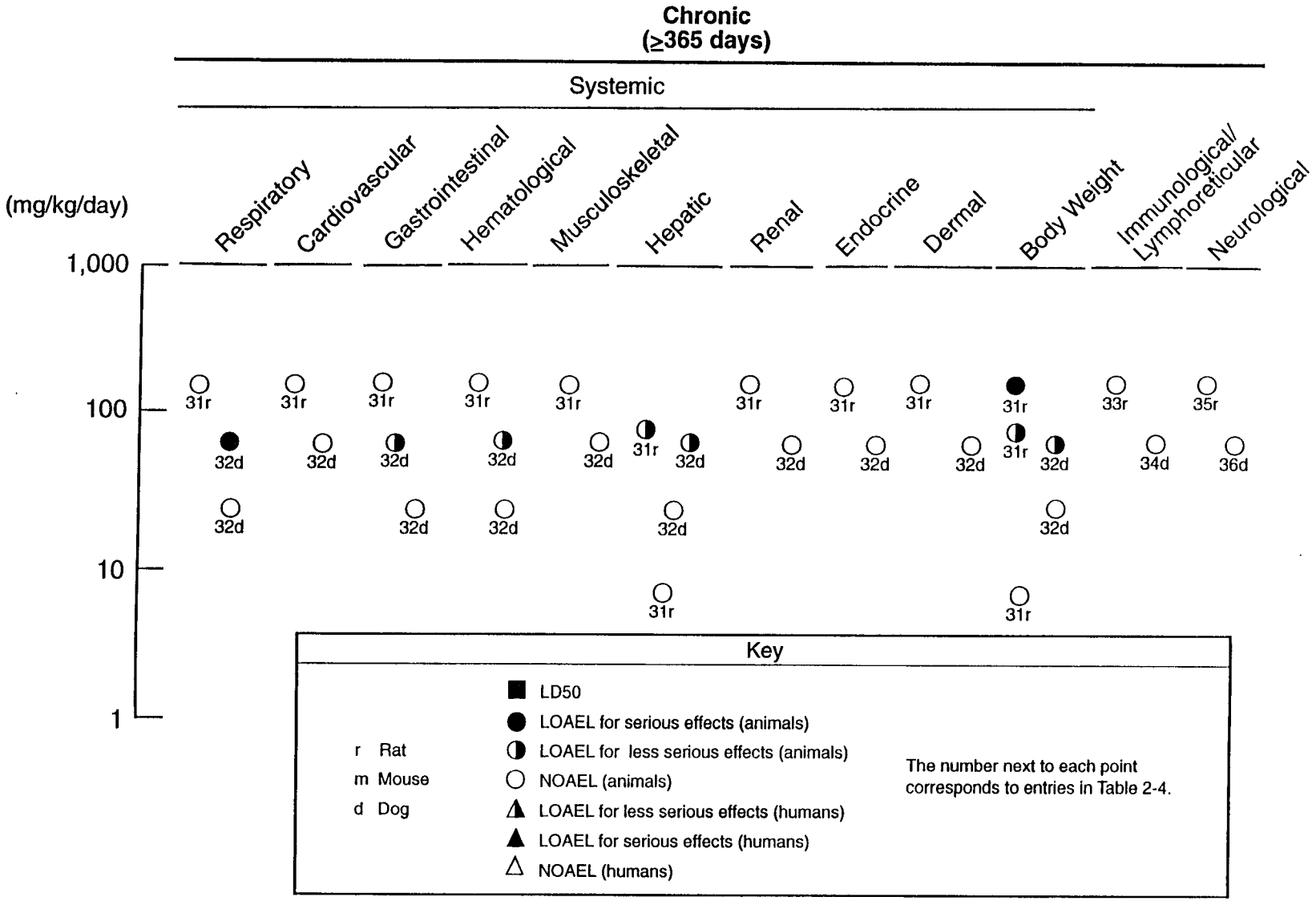


Figure 2-2. Levels of Significant Exposure to Nickel– Oral (continued)



infiltration of the lungs was observed at 20 mg nickel/kg/day. This study is confounded by decreased food and water intake observed in exposed animals. Emphysema, bronchiolectasis, and cholesterol granulomas were also observed in dogs exposed to 62.5 mg nickel/kg/day as nickel sulfate in the diet for 2 years, but not in rats exposed at up to 187.5 mg/kg/day for 2 years (Ambrose et al. 1976).

Cardiovascular Effects. Nickel sulfate crystals (rough estimate of 570 mg nickel/kg) were accidentally ingested by a 2-year-old child (Daldrup et al. 1983). Four hours after ingestion, cardiac arrest occurred, and the child died 8 hours after exposure.

Rats exposed to 8.6 mg nickel/kg/day as nickel chloride for 91 days had decreased heart weight (American Biogenics Corporation 1988), whereas rats exposed to 75 mg nickel/kg/day as nickel sulfate for 2 years had increased heart weight (Ambrose et al. 1976). Because the changes in heart weight were not accompanied by histological changes, the significance of these changes is not known. Histological changes in the heart were not observed in rats treated with nickel chloride in the drinking water at 53 mg/kg/day for up to 30 weeks (RTI 1988a), or in dogs provided with nickel sulfate in the diet at a dose of 62.5 mg nickel/kg/day for 2 years (Ambrose et al. 1976).

Gastrointestinal Effects. Symptoms of gastrointestinal distress were reported by workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1-35.7 mg nickel/kg. The symptoms included nausea (15 workers), abdominal cramps (14 workers), diarrhea (4 workers), and vomiting (3 workers). Although the actual contribution of boric acid to these effects is not known, the investigators (Sunder-man et al. 1988) indicate that the intake of 20-200 mg boric acid probably did not contribute to the observed effects because the effects of boric acid are generally observed only following ingestion of ≥4 g by adults.

Gastrointestinal effects were observed in 6/52 rats that died following treatment by gavage with 25 mg nickel/kg/day as nickel chloride hexahydrate for up to 91 days (American Biogenics Corporation 1988). The effects included discolored gastrointestinal contents, ulcerative gastritis, and enteritis. Discolored (green) gastrointestinal contents were also observed at 1.2 and 8.6 mg/kg/day. The discoloration may have been due to the presence of nickel chloride in the gastrointestinal tract.

Gastrointestinal effects were not observed in rats treated with nickel sulfate in the diet at 187.5 mg nickel/kg/day for 2 years (Ambrose et al. 1976). During the first 3 days of a 2-year study, dogs vomited following treatment with nickel sulfate in the diet at 62.5 mg nickel/kg/day (Ambrose et al. 1976). The dose was lowered to 37.5 mg nickel/kg/day for 2 weeks, and then incrementally raised at 2-week intervals back to 62.5 mg/kg/day, at which time no further gastrointestinal distress was noted. These studies indicate that high doses of nickel can be irritating to the gastrointestinal tract, although acclimation to high levels of dietary nickel can occur. The difference in the results of the American Biogenics Corporation (1988) and Ambrose et al. (1976) studies in rats is probably a result of the different routes of exposure; gavage treatment results in higher concentrations of nickel in the gastrointestinal tract than treatment in the diet.

Hematological Effects. A transient increase in blood reticulocytes was observed in workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunder-man et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1-35.7 mg nickel/kg. The contribution of boric acid to these effects is not known.

Rat studies have indicated that intermediate-duration exposure to ≥0.7 mg nickel/kg/day as various nickel salts causes hematological effects. Effects included a decrease in hemoglobin (Weischer et al. 1980; Whanger 1973) and increases in leukocyte counts (American Biogenics Corporation 1988). No hematological effects were observed in rats treated with nickel sulfate in the diet at a dose of 187.5 mg nickel/kg/day for 2 years (Ambrose et al. 1976). Low hematocrit levels were observed in dogs after chronic dietary exposure to 62.5 mg nickel/kg/day as nickel sulfate (Ambrose et al. 1976).

Musculoskeletal Effects. Muscular pain was reported by one worker who drank water contaminated with nickel sulfate, nickel chloride, and boric acid during one work shift (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1-35.7 mg nickel/kg. The contribution of boric acid to these effects is not known.

Microscopic changes in skeletal muscle were not observed in rats or dogs fed nickel sulfate in the diet at doses up to 187.5 mg nickel/kg/day for rats and 62.5 mg nickel/kg/day for dogs (Ambrose et al. 1976).

Hepatic Effects. A transient increase in serum bilirubin was observed in 3 of 10 workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). The workers who reported symptoms (20 of 35) or were hospitalized (10 of 35) were exposed to an estimated dose of 7.1-35.7 mg nickel/kg. The contribution of boric acid to these effects is not known.

Decreased liver weight was observed in rats and mice exposed to ≥1.5 mg nickel/kg/day as nickel chloride or nickel sulfate for ≤2 years (Ambrose et al. 1976; American Biogenics Corporation 1988; Dieter et al. 1988; Weischer et al. 1980). A significant increase in relative liver weight, however, was observed in dogs exposed to 62.5 mg nickel/kg/day as nickel sulfate for 2 years (Ambrose et al. 1976). Because histological changes in the liver were not observed in these studies, the significance of the liver weight changes is unclear.

Renal Effects. A transient increase in urine albumin was observed in 3 of 10 workers who were hospitalized after drinking water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The workers who reported symptoms were exposed to an estimated dose of 7.1-35.7 mg nickel/kg. The contribution of boric acid to these effects is not known.

Renal tubular damage at the corticomedullary junction described as minor was observed in mice exposed to ≥108 mg nickel/kg/day as nickel sulfate in the drinking water for 180 days (Dieter et al. 1988). The renal effects included the loss of renal tubular epithelial cells and the presence of hyaline casts in the tubule (suggesting protein loss). No changes in markers of renal tubular function (urinary lactate dehydrogenase, NAG, β_2-microglobulin) were observed in rats exposed to nickel sulfate in the drinking water for 6 months at a concentration that supplied doses of 6.9 mg/kg/day for males and 7.6 mg/kg/day for females (Vyskocil et al. 1994b). Urinary albumin, a marker of glomerular barrier dysfunction, was significantly increased in nickel-exposed female rats. Albumin excretion also tended to be higher in male rats but did not reach statistical

significance because of two control rats with very high values. The investigators noted that male rats develop a spontaneous nephrosis as they age and that this may have obscured the effect of nickel.

In dogs, polyuria and increased kidney weight were observed after exposure to 62.5 mg nickel/kg/day as nickel sulfate for 2 years; however, renal effects were not observed in similarly treated rats (Ambrose et al. 1976). Changes in kidney weight (both increases and decreases) were observed in rats exposed to ≥1.5 mg nickel/kg/day as nickel salts for 19 months (American Biogenics Corporation 1988; RTI 1988b; Weischer et al. 1980). The toxicological significance of these data is not known.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to nickel.

Although histological changes were not observed, increases in pituitary weights were observed in male but not female rats treated with nickel chloride at doses ≥20 mg nickel/kg/day for up to 30 weeks (RTI 1986, 1988a, 1988b). The multigeneration study (RTI 1988a, 1988b) is confounded by a decrease in both food and water intake. Decreased prolactin levels were observed in female rats treated with 31 mg nickel/kg/day as nickel chloride in the drinking water throughout the breeding and lactation of two litters (11 weeks before breeding, 2-week rest period after weaning of the first litter, followed by a second breeding) but not at a 6.8-mg/kg/day dose (Smith et al. 1993). Histological examinations did not reveal any effects in the pituitary, thyroid, and adrenal glands or in the pancreas of rats and dogs treated with nickel sulfate in the diet for 2 years at 187.5 mg nickel/kg/day for rats and 62.5 mg nickel/kg/day for dogs (Ambrose et al. 1976).

Dermal Effects. Contact dermatitis, which results from dermal exposure to nickel, is the most prevalent effect of nickel in the general population (see Section 2.2.3.2). Several studies indicate that a single oral dose of nickel given as nickel sulfate can result in a flare-up in the dermatitis in nickel-sensitive individuals (Burrows et al. 1981; Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Kaaber et al. 1978; Veien et al. 1987). The lowest single dose resulting in dermatitis, including erythema on the body, worsening of hand eczema, and a flare-up at the patch test site, was 0.009 mg nickel/kg (Cronin et al. 1980). Limitations of these studies include small sample size, the observation of placebo effects, non-double-blind studies (possibly introducing

investigator bias), and inadequate reporting of whether subjects were fasted overnight or whether there were other dietary restrictions (IRIS 1996). Although some sensitive individuals may react to very low oral doses of nickel, Menne and Maibach (1987) concluded that only a minor number of nickel-sensitive patients react to oral doses below 1.25 mg (0.02 mg/kg), but nearly all will react at 5.5 mg (0.08 mg/kg).

Nielsen et al. (1990) fed 12 women with hand eczema and known allergy to nickel a diet (oatmeal, soy beans, cocoa) with five times the normal level of nickel (about 0.007 mg/kg/day) for 4 days. An aggravation of hand eczema was found in 602 by day 4 after the start of the challenge, and although excess nickel was excreted by 2 days after the last treatment, further exacerbation of hand eczema was observed in l0/12 by day 11. It is not clear how well the diets were controlled after the challenge period, and the subjects may have eaten foods that contained vasoactive substances that could exacerbate an allergic reaction. This study also suggests that withdrawal of nickel rather than the peak nickel levels may contribute to the dermatitis observed in some sensitive individuals.

Intermediate-duration studies suggest that longer term oral exposure can be tolerated by some nickel-sensitive individuals and may even serve to desensitize some individuals. Jordan and King (1979) found flaring of dermatitis in only l/10 nickel-sensitive women given nickel sulfate at 0.007 mg/kg/day for 2 weeks. Patch test responses to nickel were reduced in nickel-sensitive women given one weekly dose of 0.05 or 0.07 (but not 0.007) mg nickel/kg as nickel sulfate for 6 weeks (Sjovall et al. 1987). Santucci et al. (1994) gave increasing daily doses of nickel (0.01-0.03 mg/kg/day) as nickel sulfate to eight nickel-sensitive women for up to 178 days. A significant clinical improvement in hand eczema was observed in all subjects after 1 month of treatment, and continued treatment resulted in healing of all dermal lesions except for those on the hands. Measurement of urine and serum nickel suggested a decrease in the absorption of nickel and an increase in the excretion of nickel with longer exposure. The Santucci et al. (1994) study indicates that a daily dose of 0.01-0.03 mg nickel/kg can be tolerated by some nickel-sensitive people and may also serve to reduce their sensitivity. Among 44 sensitive subjects treated with a regimen of l-2 ng nickel sulfate every other day, or daily for up to 2-3 years, 7 stopped the treatment for unspecified reasons, 7 had reactivation of symptoms, and complete (29) or partial (1) disappearance of symptoms for 24 years was observed in 30 subjects. In guinea pigs sensitized before oral treatment with nickel, only a transient desensitization was observed (van Hoogstraten et al. 1994).

Oral exposure before the sensitizing exposure may also help prevent nickel sensitization in some individuals. A study of 2,159 subjects examining the relationship between ear piercing and orthodontic treatment found that nickel sensitivity was reduced when orthodontic treatment preceded ear piercing (23.3% versus 38.1%, $p<0.005$) (van Hoogstraten et al. 1994). The investigators hypothesized that the oral nickel exposure that occurred during orthodontic treatment helped prevent the sensitization that occurred following ear piercing with earrings containing nickel. Orthodontic treatment after ear piercing did not affect the risk of nickel sensitization. Further evidence that oral exposure to nickel before a sensitizing exposure can prevent hypersensitivity is provided by the observation that nickel sensitivity in mice could be consistently produced only when metal frames to cover the cages and metal water nipples that released nickel were replaced with glass covers and nipples free of nickel (van Hoogstraten et al. 1994). Oral treatment of guinea pigs with nickel sulfate (30 mg/week for 6 weeks) has also been shown to prevent dermal sensitization (van Hoogstraten et al. 1994). Skin exposure of guinea pigs to nickel (non-sensitizing contacts) before oral exposure was also shown to interfere with oral tolerance induction.

Histological changes in the skin have not been observed in rats treated by gavage with nickel chloride at a dose of 8.6 mg nickel/kg/day for 91 days (American Biogenics Corporation 1988), or in rats and dogs exposed to nickel sulfate in the diet for 2 years at doses of 187.5 and 62.5 mg nickel/kg/day, respectively (Ambrose et al. 1976). These studies suggest that the skin is not affected by orally administered nickel in animals that have not been previously sensitized to nickel.

Ocular Effects. In a pharmacokinetic study in humans, transient left homonymous hemianopsia (loss of sight in the corresponding lateral half of the eyes) occurred in one male subject following ingestion of 0.05 mg nickel/kg as nickel sulfate in the drinking water (Sunderman et al. 1989b). No adverse effects were found in other subjects (n=9) when lower doses of 0.018 and 0.012 mg nickel/kg were used. This neurological effect on vision is discussed in Section 2.2.2.4. and is recorded in Table 2-4 and Figure 2-2 under Neurological Effects.

No treatment-related ophthalmological changes were observed in rats treated by gavage with 8.6 mg nickel/kg/day as nickel chloride for 91 days (American Biogenics Corporation 1988).

Body Weight Effects. Decreased body weight gain of 10% or more, associated with reduced food and/or water intake, has been observed in rats treated by gavage with nickel chloride at 8.6 mg nickel/kg/day for 91 days (American Biogenics Corporation 1988), in rats treated with nickel chloride in the drinking water at 0.38 mg nickel/kg/day for 28 days (Weischer et al. 1980) or 53 mg nickel/kg/day for 30 weeks (RTI 1988a), and in rats treated with nickel sulfate in the diet at 75 mg nickel/kg/day for 2 years (Ambrose et al. 1976). Decreased body weight gain has also been reported in mice treated with nickel sulfate in drinking water at a dose of 108 mg nickel/kg/day for 180 days (Dieter et al. 1988), and in dogs treated with nickel sulfate in the diet at a dose of 62.4 mgfkglday for 2 years (Ambrose et al. 1976). Decreases in body weight gain of 10% or more were not observed in female rats treated with nickel chloride in the drinking water at 31.6 mg nickel/kg/day for 11 weeks (Smith et al. 1993), or with nickel chloride at a dose of 7.6 mg nickel/kg/day for 3 or 6 months (Vyskocil et al. 1994b).

2.2.2.3 Immunological and Lymphoreticular Effects

Dermatitis resulting from nickel allergy is well reported in the literature (see Section 2.2.2.2 for further discussion of allergic dermatitis following oral exposure).

Effects on the immunological system following exposure to ≥44 mg nickel/kg/day as nickel sulfate in the drinking water for 180 days were assessed in mice (Dieter et al. 1988). The immunological effects included a dose-related decrease in the spleen lymphoproliferative response to a B-cell mitogen, a significant decrease in spleen and bone marrow cellularity, and dose-related reductions in the bone marrow proliferative response. When challenged with coxsackie virus B3, an enhanced inflammatory response was observed in the hearts of mice treated with nickel chloride in drinking water at 20.3 mg nickel/kg/day for 10-11 weeks (Ilback et al. 1994). Nickel treatment had no effect on virus-induced lethality, spleen or thymus weights, or the number of cells in the spleen or thymus. Gross and microscopic examinations of the spleen did not reveal any adverse effects in rats or dogs fed nickel sulfate in the diet for 2 years at doses of 187.5 mg/kg/day for rats and 62.5 mg/kg/day for dogs (Ambrose et al. 1976).

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species, duration category, and nickel compound are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

Neurological effects were observed in workers who drank water during one work shift from a water fountain contaminated with nickel sulfate, nickel chloride, and boric acid (Sunderman et al. 1988). Thirty-five workers were exposed, 20 reported symptoms, and 10 were hospitalized. The dose to which the workers with symptoms were exposed was estimated to be 7.1-35.7 mg nickel/kg. The neurological effects included giddiness (7 workers), weariness (6 workers), and headache (5 workers). The contribution of boric acid to these effects is not known.

In a study designed to determine the absorption and elimination of nickel in humans, one male volunteer who ingested a single dose of 0.05 mg nickel/kg as nickel sulfate in drinking water developed left homonymous hemianopsia (loss of sight in the corresponding lateral half of the eyes) 7 hours later; the condition lasted for 2 hours (Sunderman et al. 1989b). The loss of sight occurred soon after the peak serum concentration of nickel was reached, leading the investigators to suspect a causal relationship between nickel exposure and the loss of sight. The doses given to other subjects were lowered to 0.018 and 0.012 mg nickel/kg with no adverse effects.

In a 90-day study, lethargy, ataxia, prostration, irregular breathing, and cool body temperature were observed in rats treated by gavage with nickel chloride (American Biogenics Corporation 1988). These effects were observed frequently at 25 mg nickel/kg/day, a dose at which all rats died, and at lower incidences at 8.6 mg nickel/kg/day, a dose at which 6/52 rats died. At the lower dose, it is not clear if the neurological effects were observed only in the animals that died. No signs of neurological dysfunction were observed at 1.2 mg/kg/day. Microscopic examinations did not reveal any changes in the brains of rats or dogs treated with nickel salts at doses ≥8.6 mg nickel/kg/day for up to 2 years (Ambrose et al. 1976; American Biogenics Corporation 1988).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species, duration category, and nickel compound are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to nickel.

An increase in abnormalities was observed in spermatozoa from mice treated orally with a single dose of nickel sulfate (28 mg nickel/kg), nickel nitrate (23 mg nickel/kg), or nickel chloride (43 mg nickel/kg) (Sobti and Gill 1989). The increase in abnormalities was greatest (3.7-fold) following exposure to nickel nitrate. Spermatozoa were examined 5 weeks after treatment. The specific route of exposure was not given; however, because mg/kg doses were reported, it was assumed that treatment was by gavage. This study is also limited by the use of only one dose of each nickel compound.

Multigeneration studies of nickel in rats suggest that high-dose oral exposure to nickel may adversely affect reproduction. Ambrose et al. (1976) found a dose-related increase in the number of stillborn pups in the F_1 but not the F_2 generation in a multigeneration study in which the rats were fed nickel chloride in the diet at 0, 22.5, 45, or 90 mg nickel/kg/day. The number of offspring weaned also decreased with increasing doses of nickel. Both the parental and F_1 generations were treated for 11 weeks before mating. The proportion of litters delivered after gestation day 21 was increased in rats treated with nickel chloride in the drinking water at 31 mg nickel/kg/day, and an increase in postnatal mortality was noted at about 50 mg nickel/kg/day (RTI 1988a, 1988b). As previously indicated (see Section 2.2.2.1), maternal deaths at the time of parturition were observed only in nickel-treated rats (RTI 1988a, 1988b). This two-part study is confounded by decreases in food and water intake as well as transient increases in temperature (as much as 10°F) and decreases in humidity. EPA concluded that effects observed at the two lower doses of about 31 and 53 mg/kg/day could not be considered to be genuine adverse effects (IRIS 1996). This study is not presented in Table 2-4 and Figure 2-2 under reproductive effects. A two-litter study, which is not confounded by changes in temperature and humidity, confirms that high oral doses of nickel increase the number and the proportion per litter of pups born dead or dying shortly after birth (Smith et al. 1993). The rats were treated for 11 weeks prior to breeding. In the first litter the percentages of dead pups per litter were 5%, 9%, 0%, and 35%, and in the second litter the percentages of dead pups per litter were 2%, 1l%, 16%, and 22% in rats given nickel chloride in the drinking water at 0, 1.3, 6.8, and 31.6 mg nickel/kg/day, respectively. The investigators (Smith et al. 1993) concluded that the low dose was a LOAEL that caused a disturbance in the normal

physiological progression of events during late gestation, birth, and the early postnatal period. The shallow dose-response curve at the lower doses was attributed to a possible homeostatic mechanism regulating nickel absorption that was only overwhelmed at the high dose.

An increase in the number of spontaneous abortions was observed in mice treated on gestation days 2-17 with nickel chloride in the drinking water at 160 mg nickel/kg/day, but no increase was observed at 80 mg nickel/kg/day (Berman and Rehnberg 1983). Microscopic examination of the testes and ovaries of rats and dogs treated orally for up to 2 years with nickel salts at doses up to 187.5 mg nickel/kg/day for rats and 62.5 mg nickel/kg/day for dogs did not reveal any effects (Ambrose et al. 1976; American Biogenics Corporation 1988; RTI 1986, 1988a, 1988b).

The highest NOAEL value and all LOAEL values from each reliable study for reproductive effects in each species, duration category, and nickel compound are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to nickel.

In a developmental screening test in mice, no effects on the average number of neonates per litter or on the average weights of the neonates were observed when dams were treated by gavage on gestation days 8-12 with 90.6 mg nickel/kg/day as nickel chloride (a dose that resulted in a significant decrease in maternal body weight) (Seidenberg et al. 1986). No effects on figure eight maze reactive locomotor activity levels were observed in the offspring of mice treated by gavage at 45.3 mg nickel/kg/day as nickel chloride on gestation days 8-12 (Gray et al. 1986).

As indicated in the reproductive effects section, multigeneration and multilitter studies in rats have shown that nickel affects the time of gestation, birth, and the early postnatal period, reducing the number of live offspring born and the number surviving through lactation (Ambrose et al. 1976; RTI 1988a, 1988b; Schroeder and Mitchener 1971; Smith et al. 1993). Although offspring body weights were significantly reduced at 53 mg nickel/kg/day (RTI 1988a), no teratogenic effects were reported in any of these studies.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species, duration category, and nickel compound are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to nickel. Increases in micronuclei in the bone marrow were observed in mice treated orally with nickel sulfate (28 mg nickel/kg), nickel nitrate (23 mg nickel/kg), or nickel chloride (43 mg nickel/kg) (Sobti and Gill 1989). The specific route of exposure was not given; however, because mg/kg doses were reported, it was assumed that the mice were administered a single oral dose by gavage with a nickel compound in water. Bone marrow cells were examined 6 or 30 hours after the mice were treated. This study is also limited by the use of only one dose of each nickel compound.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to nickel.

In lifetime drinking water studies in rats and mice, nickel acetate (0.6 mg nickel/kg/day for rats; 0.95 mg nickel /kg/day for mice) was found to be noncarcinogenic (Schroeder et al. 1964, 1974). The incidence of tumors was comparable to that observed in controls.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals after dermal exposure to nickel.

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, or ocular effects in humans or animals after dermal exposure to nickel.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects for each species, duration category, and nickel compound are recorded in Table 2-5.

Respiratory Effects. Scratch tests and intradermal tests were performed on a patient diagnosed with nickel-related asthma (McConnell et al.1973). Nonasthmatic controls were also tested. Testing resulted in respiratory distress in the patient but not in the controls, with a more severe response resulting from the scratch test.

No studies were located regarding respiratory effects in animals after dermal exposure to nickel.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to nickel.

Hematocrit and hemoglobin levels were not affected in guinea pigs treated with 100 mg nickel/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994). Only one dose level was used in this study.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to nickel.

Effects on the liver were observed in rats treated dermally (lateral abdominal area) with daily doses of 60 mg nickel/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). The effects included swollen hepatocytes and feathery degeneration after 15 days and focal necrosis and vacuolization after 30 days. In this study, there was no indication that the rats were prevented from licking the nickel from the skin; therefore, these effects could have resulted from oral

TABLE 2-5. Levels of Significant Exposure to Nickel - Dermal

Species/ (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference/ Chemical form
ACUTE EXPOSURE						
Systemic						
Human	once	Derm	0.01%	0.0316% (contact dermatitis in sensitive individuals)		Emmett et al. 1988 sulfate
Human	once	Derm		0.04% (allergic dermatitis in sensitive individuals)		Eun and Marks 1990 sulfate
Human	once	Derm	0.01%	0.1% (skin reaction in nickel sensitive individuals)		Menne and Calvin 1993 chloride
Human	once	Derm		>1 $\mu g/cm^2/wk$[a] (contact dermatitis)		Menne et al. 1987
Immuno/Lymphor						
Mouse (C3H:Hej)	once occluded for 7d			1% F (develpoment of dermal sensitization)		Siller and Seymour 1994 sulfate

TABLE 2-5. Levels of Significant Exposure to Nickel - Dermal (continued)

Species/ (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference/ Chemical form
INTERMEDIATE EXPOSURE						
Systemic						
Rat (NS)	15 or 30d daily	Hepatic	40 M mg/kg/d	60 M mg/kg/d (focal necrosis)		Mathur et al. 1977 sulfate
		Renal	100 M mg/kg/d			
		Derm		40 M mg/kg/d (slight hyperkeratosis)	60M mg/kg/d (degeneration of basal layer)	
Gn Pig (NS)	15 or 30d	Hemato	100 mg/kg/d			Mathur and Gupta 1994 sulfate
		Hepatic		100 mg/kg/d (increased Mg^{2+} ATPase, acid phosphatase, and glucose-6-phosphatase activities)		
		Renal		100 mg/kg/d (increased Mg^{2+} ATPase activity)		
		Endocr		100 mg/kg/d (increased blood glucose)		
Reproductive						
Rat (NS)	30 d daily		40 M mg/kg/d		60M mg/kg/d (degeneration and edema of seminiferous tubules)	Mathur et al. 1977 sulfate

[a]Menne et al. (1987) reported that nickel alloys which released more than 1 $\mu g/cm^2/wk$ caused contact dermatitis in sensitive individuals.

d = day(s); Derm = dermal; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; ppm = parts per million

exposure. Increased Mg^{2+} ATPase was observed in the livers of guinea pigs treated with 100 mg nickel/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994). Acid phosphatase and glucose-6-phosphatase activities were increased only after 30 days of treatment.

Renal Effects. Proteinuria was not observed in electroforming industry workers exposed to nickel. No information was provided on exposure level or nickel compound (Wall and Calnan 1980).

No gross or microscopic lesions were observed in the kidneys of rats treated dermally with ≤100 mg nickel/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). In this study, there was no indication that the rats were prevented from licking the nickel from the skin; therefore, the animals could have been orally exposed. Increased Mg^{2+} ATPase was observed in the kidneys of guinea pigs treated with 100 mg nickel/kg/day as nickel sulfate placed on skin of the back for 30 days (Mathur and Gupta 1994). No effect was noted at 15 days, and dermal nickel exposure had no effect on kidney acid phosphatase or glucose-6-phosphatase activities.

Endocrine Effects. No studies were located regarding endocrine effects in humans after dermal exposure to nickel.

Blood glucose was significantly increased in guinea pigs treated with 100 mg nickel/kg/day as nickel sulfate placed on skin of the back for 15 or 30 days (Mathur and Gupta 1994).

Dermal Effects. An allergy to nickel is the most frequent contact allergy in women. Exposure to nickel in consumer products, especially jewehy, rather than occupational exposure is often the sensitizing exposure. An association has been observed between ear piercing and nickel sensitivity (Dotterud and Falk 1994; Larsson-Stymne and Widstrom 1985; Meijer et al. 1995). The prevalence of nickel allergy was 9% among girls (age 8, 11, 15; n=960) with pierced ears compared to 1% among girls without pierced ears. Girls with more than one hole in each ear were also more likely to be sensitive to nickel than girls with only one hole in each ear (19% versus 11%) (Larsson-Stymne and Widstrom 1985). In a study in schoolchildren age 7-12, the frequency of nickel allergy was 30.8% among girls with pierced ears and 16.3% among girls who did not have pierced ears (Dotterud and Falk 1994). Among a group of Swedish men (age 18-24) completing military

service, 4.6% with pierced ears reacted to nickel, while 0.8% who did not have pierced ears had a positive reaction to nickel (Meijer et al. 1995). Once an individual is sensitized, even minimal contact with nickel may cause a reaction. Keczkes et al. (1982) have shown that sensitivity to nickel remains for many years. Fourteen people who tested positively for nickel sensitivity using nickel sulfate also tested positive 10 years later.

Patch test studies in sensitive individuals using nickel sulfate have shown a dose-response relationship between the amount of nickel and the severity of the test response (Emmett et al. 1988 Eun and Marks 1990). In a study of 12 individuals, a nickel concentration of 0.0316% (316 ppm) in petrolatum resulted in dermatitis, while a concentration of 0.01% (100 ppm) did not produce adverse effects (Eun and Marks 1990). The NOAEL concentration in aqueous solution was 0.0316% (316 ppm).

Although most patch testing is done with nickel sulfate because it is less irritating than nickel chloride, exposure of the skin to nickel alloys results in the release of nickel chloride from the influence of human sweat. Therefore, nickel chloride is the more relevant form of nickel for examining threshold concentrations (Menne 1994). Menne and Calvin (1993) examined skin reactions to various concentrations of nickel chloride in 51 sensitive and 16 nonsensitive individuals. Although inflammatory reactions in the sweat ducts and hair follicles were observed at 0.01% and lower, positive reactions to nickel were not observed. To be scored as a positive reaction, the test area had to have both redness and infiltration, while the appearance of vesicles and/or a bullous reaction were scored as a more severe reaction. At 0.l%, 4/51 and l/51 tested positive with and without 4% sodium lauryl sulfate. Menne et al. (1987) examined the reactivity to different nickel alloys in 173 nickel-sensitive individuals. With one exception (Inconel 600), alloys that released nickel into synthetic sweat at a rate of <0.5 $\mu g/cm^2$/week showed weak reactivity, while alloys that released nickel at a rate of $>l$ $\mu g/cm^2$/week produced strong reactions.

Nickel sensitivity has been induced in guinea pigs following skin painting or intradermal injection with nickel sulfate (Turk and Parker 1977; Wahlberg 1976; Zissu et al. 1987). As discussed in Section 2.2.2.2, nickel sensitivity can also be induced in mice if oral exposure to nickel is reduced (Moller 1984; van Hoogstraten et al. 1994).

Effects on the skin were observed in rats treated dermally with ≥40 mg nickel/kg/day as nickel sulfate for 15 or 30 days (Mathur et al. 1977). The effects included distortion of the epidermis and dermis after 15 days and hyperkeratinization, vacuolization, hydropic degeneration of the basal layer, and atrophy of the epidermis at 30 days. Biochemical changes in the skin (enzymatic changes, increased lipid peroxidation, and an increase in the content of sulfhydryl groups and amino nitrogen) were observed in guinea pigs dermally exposed to nickel sulfate for up to 14 days (Mathur et al. 1988, 1992). Additive effects were observed when nickel sulfate was given in combination with sodium lauryl sulfate.

2.2.3.3 Immunological and Lymphoreticular Effects

Contact dermatitis resulting from nickel allergy is well reported in the literature (see Section 2.2.3.2 for further discussion of allergic reactions to nickel following dermal exposure). A relationship between human lymphocyte antigens (HLA) and nickel sensitivity was observed in individuals who had contact allergic reactions and positive results in the patch test (Mozzanica et al. 1990). The individuals had not been occupationally exposed to nickel. The HLA typing found a significantly greater prevalence of HLA-DRw6 antigen in the nickel-sensitive group compared to normal controls. The relative risk for individuals with DRw6 to develop a sensitivity to nickel was approximately 1:11. In individuals with allergic contact dermatitis to nickel, nickel directly bound and activated T-cells (Kapsenberg et al. 1988).

The dose-response relationship for the development of nickel sensitivity has been examined in a mouse model (Siller and Seymour 1994). The sensitization exposure involved placing a 6-mm pad containing 45 μL of a 0%, l%, 5%, l0%, 15%, or 20% nickel sulfate solution on the shaved abdominal skin of mice. This pad was left on the skin under occlusion for 7 days. Seven days after the sensitization procedure, the mice were challenged with 10 μL of a 0.4% aqueous nickel sulfate solution injected into the footpad. Saline was injected into the opposite footpad as a control. Contact hypersensitivity, indicated by footpad swelling, was elicited at all doses, although the degree of swelling was minimal and only barely significant at 48 hours at the 1% concentration. Footpad swelling increased as the sensitizing dose increased and generally peaked between 24 and 48 hours after the challenge. In a comparison of the responses between male and female mice, males showed a weaker and more variable response than females, and the response peaked at

72 hours in males compared to 48 hours in females. The LOAEL for sensitization in mice is recorded in Table 2-5.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after dermal exposure to nickel.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to nickel.

Tubular degeneration of the testes was observed in rats treated dermally with nickel sulfate at 60 mg nickel/kg/day for 30 days (Mathur et al. 1977). No effects were found at 40 mg nickel/kg/day after 30 days or at doses of ≤100 mg nickel/kg/day after 15 days of treatment. In this study, there was no indication that the rats were prevented from licking the nickel sulfate from the skin; therefore, these effects could have resulted from oral exposure. Consequently, these values do not appear in Table 2-5.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to nickel.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to nickel.

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to nickel.

2.3 TOXICOKINETICS

Following inhalation exposure, about 20-35% of nickel deposited in the lungs of humans is absorbed into the bloodstream. Absorption from the respiratory tract is dependent on the solubility of the nickel compound, with higher urinary nickel observed in workers exposed to soluble nickel compounds (nickel chloride, nicke sulfate) than in those exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide). Following oral exposure, about 27% of the nickel given to humans in drinking water was absorbed, while only about 1% was absorbed when nickel was given with food. Nickel applied directly to the skin can be absorbed into the skin where it may remain rather than entering the bloodstream.

Autopsy data from nonoccupationally exposed individuals indicate that the highest concentrations of nickel are found in the skin, adrenal glands, and intestines. Following inhalation exposure, nickel also tends to accumulate in the lungs. The pituitary may accumulate nickel if exposure occurs during pregnancy. Nickel has been shown to cross the placenta, and nickel can accumulate in milk, resulting in exposure of the offspring. In human serum, the exchangeable pool of nickel is bound to albumin, $_{L}$-histidine, and α_2-macroglobulin. There is also a nonexchangeable pool of nickel in the serum which is tightly bound to nickeloplasmin. Regardless of the route of exposure, absorbed nickel is excreted in the urine. Nickel that is not absorbed from the gastrointestinal tract is excreted in the feces.

2.3.1 Absorption

2.3.1 .I inhalation Exposure

Inhaled nickel particles are deposited in the upper and lower respiratory tract and are subsequently absorbed by several mechanisms. The deposition pattern in the respiratory tract is related to particle size, which determines the degree to which particles are affected by inertial impaction, sedimentation, and diffusion. Large particles (5-30 μm) deposit in the nasopharyngeal area where

higher airstream velocities and airway geometry promote inertial impaction (Gordon and Amdur 1991). Smaller particles (1-5 μm) enter the trachea and bronchiolar region where they deposit principally by sedimentation. The smallest particles (<1 μm) enter the alveolar region of the lungs where diffusion and electrostatic precipitation of the particles occurs. Fractional deposition can be expected to vary considerably with age and breathing patterns.

In humans, about 20-35% of the inhaled less-soluble nickel that is retained in the lungs is absorbed into the blood (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991). The remainder is either swallowed, expectorated, or remains in the respiratory tract. Nickel is detected in the urine of workers exposed to nickel (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Higher concentrations of urinary nickel were found in workers exposed to soluble nickel compounds (nickel chloride, nickel sulfate) than in those exposed to less-soluble nickel compounds (nickel oxide, nickel subsulfide), indicating that the soluble compounds were more readily absorbed from the respiratory tract (Torjussen and Andersen 1979). A man that died of adult respiratory distress syndrome 13 days after being exposed to a very high concentration of metallic nickel fume, had very high concentrations of nickel in his urine (Rendall et al. 1994). This case report indicates that metallic nickel can be absorbed from the lungs if levels are high enough to result in lung damage.

The half-life of nickel in the lungs of rats exposed by inhalation has been reported to be 32 hours for nickel sulfate (mass median aerodynamic diameter [MMAD] 0.6 μm) (Hirano et al. 1994b), 4.6 days for nickel subsulfide ($^{63}Ni_3S_2$ activity, median aerodynamic diameter [AMAD] 1.3 μm), and 120 days for green nickel oxide (^{63}NiO, AMAD 1.3 μm) (Benson et al. 1994). Elimination halftimes from the lung of rats of 7.7, 11.5, and 21 months were calculated for green nickel oxide with MMADs of 0.6, 1.2, and 4.0 μm, respectively (Tanaka et al. 1985, 1988).

Following exposure to green nickel oxide, nickel was only excreted in the feces indicating that the dominant mechanism for removing nickel oxide from the lungs is macrophage mediated rather than dissolution-absorption (Benson et al. 1994). Following exposure to nickel subsulfide, nickel was excreted in both the urine and the feces, with greater amounts in the urine on days 6-14 postexposure. These results indicate that dissolution-absorption plays an important role in the removal of nickel subsulfide in the lungs, and the study authors concluded that in the lungs nickel subsulfide acts more like a soluble compound (Benson et al. 1994).

2.3.1.2 Oral Exposure

Human absorption studies show that 40 times more nickel was absorbed from the gastrointestinal tract when nickel sulfate was given in the drinking water (27±17%) than when it was given in food (0.7±0.4%) (Sunderman et al. 1989b). The bioavailability of nickel, as measured by serum nickel levels, was elevated in fasted subjects given nickel sulfate in drinking water (peak increase of 80 μg/L after 3 hours), but not when nickel was given with food (Solomons et al. 1982). The bioavailability of nickel increased when nickel was administered in a soft drink but decreased when nickel was given with whole milk, coffee, tea, or orange juice. Ethylenediamine tetraacetic acid (EDTA) added to the diet decreased nickel bioavailability to below fasting levels (Solomons et al. 1982). Absorption of 4.3% of the given dose of nickel was estimated in eight subjects who were instructed to eat about the same amount and type of liquids and food (Christensen and Lagesson 1981). These data indicate that the presence of food profoundly reduced the absorption of nickel. The observation of a decreased serum-nickel to urine-nickel ratio with increasing nickel doses in nickel-sensitive individuals suggests that at least some sensitive people adapt to increasing oral doses of nickel by reducing absorption by the gastrointestinal tract (Santucci et al. 1994). Urinary excretion of nickel following a single oral dose given to women after an overnight fast was found to decrease with increasing age, suggesting that nickel absorption may decrease with age (Hindsen et al. 1994).

Studies in rats and dogs indicate that l-10% of nickel, given as nickel, nickel sulfate, or nickel chloride in the diet or by gavage, is rapidly absorbed by the gastrointestinal tract (Ambrose et al. 1976; Ho and Furst 1973; Tedeschi and Sunderman 1957). In a study in which rats were treated with a single gavage dose of a nickel compound (10 mg nickel) in a 5% starch saline solution, the absorption was found to be directly correlated with the solubility of the compound (Ishimatsu et al. 1995). The percentages of the dose absorbed were 0.01% for green nickel oxide, 0.09% for metallic nickel, 0.04% for black nickel oxide, 0.47% for nickel subsulfide, 11.12% for nickel sulfate, 9.8% for nickel chloride, and 33.8% for nickel nitrate. Absorption was higher for the more-soluble nickel compounds. Unabsorbed nickel is excreted in the feces.

2.3.1.3 Dermal Exposure

Human studies show that nickel can penetrate the skin (Fullerton et al. 1986; Norgaard 1955). In a study in which radioactive nickel sulfate was applied to occluded skin, 55-77% was absorbed within 24 hours, with most being absorbed in the first few hours (Norgaard 1955). It could not be determined whether the nickel had been absorbed into the deep layers of the skin or into the bloodstream. Compared to normal subjects, nickel absorption did not differ in nickel-sensitive individuals. In a study using excised human skin, only 0.23% of an applied dose of nickel chloride permeated skin after 144 hours when the skin was not occluded, while 3.5% permeated occluded skin (Fullerton et al. 1986). Nickel(II) ions from a chloride solution passed through the skin ≈50 times faster than nickel(II) ions from a sulfate solution (Fullerton et al. 1986). Application of nickel chloride in a sodium lauryl sulfate solution (0-25%, 2%, or 10%) to excised human skin resulted in a dose-related increase in the penetration of nickel during a 48-hour period (Frankild et al. 1995).

Studies in animals also indicate that nickel can penetrate the skin (Lloyd 1980; Norgaard 1957). Radioactive nickel sulfate was absorbed through the depilated skin of rabbits and guinea pigs after 24 hours and appeared primarily in the urine (Norgaard 1957). A small percentage of radioactive nickel chloride was absorbed through the skin of guinea pigs 4-24 hours after application, as indicated by radioactivity in the blood and urine (0.005-0.51%) (Lloyd 1980). Most of the nickel remained in the skin, primarily in the highly keratinized areas. Increased levels of nickel in the liver and kidney in guinea pigs treated dermally with nickel sulfate for 15 or 30 days also indicate that nickel can be absorbed through the skin (Mathur and Gupta 1994).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Workers occupationally exposed to nickel have higher lung burdens of nickel than the general population. Dry weight nickel content of the lungs at autopsy was 330±380 μg/g in roasting and smelting workers exposed to less-soluble compounds, 34±48 μg/g in electrolysis workers exposed to soluble nickel compounds, and 0.76±0.39 μg/g in unexposed controls (Andersen and Svenes 1989). Nickel levels in the lungs of cancer victims did not differ from those of other nickel workers

(Kollmeier et al. 1987; Raithel et al. 1989). Nickel levels in the nasal mucosa are higher in workers exposed to less-soluble relative to soluble nickel compounds (Torjussen and Andersen 1979). These results indicate that, following inhalation exposure, less-soluble nickel compounds remain deposited in the nasal mucosa.

Higher serum nickel levels have been found in occupationally exposed individuals compared to nonexposed controls (Angerer and Lehnert 1990; Elias et al. 1989; Torjussen and Andersen 1979). Serum nickel levels were found to be higher in workers exposed to soluble nickel compounds compared to workers exposed to less-soluble nickel compounds (Torjussen and Andersen 1979). Concentrations of nickel in the plasma, urine, and hair were similar in nickel-sensitive compared to nonsensitive individuals (Spruit and Bongaarts 1977).

Following a single 70-minute inhalation exposure of rats to green nickel oxide (^{63}NiO; 9.9 mg nickel/m^3; AMAD 1.3 μm), the fraction of the inhaled material deposited in the total respiratory tract was 0.13, with 0.08 deposited in the upper respiratory tract and 0.05 deposited in the lower respiratory tract (Benson et al. 1994). During the 180 days postexposure, nickel was not detected in extrarespiratory tract tissues. Following a single 120minute inhalation exposure of rats to nickel subsulfide ($^{63}Ni_3S_2$; 5.7 mg nickel/m^3; AMAD 1.3 μm), the fraction of inhaled material deposited in the upper respiratory tract was similar to that observed for nickel oxide (0.14 in the total respiratory tract, 0.09 in the upper respiratory tract, and 0.05 in the lower respiratory tract). In contrast to nickel from nickel oxide, nickel from nickel subsulfide was detected in the blood, kidneys, and carcass between 4 and 24 hours after the exposure.

Data in rats and mice indicate that a higher percentage of less-soluble nickel compounds was retained in the lungs for a longer time than soluble nickel compounds (Benson et al. 1987, 1988; Dunnick et al. 1989; Tanaka et al. 1985) and that the lung burden of nickel decreased with increasing particle size (≤4 μm) (Kodama et al. 1985a, 1985b). Nickel retention was ≈6 times (mice) to 10 times (rats) greater in animals exposed to less-soluble nickel subsulfide compared to soluble nickel sulfate (Benson et al. 1987, 1988). The lung burdens of nickel generally increased with increasing exposure duration and increasing levels of the various nickel compounds (Dunnick et al. 1988, 1989). From weeks 9 to 13 of exposure, lung levels of nickel sulfate and nickel subsulfide remained constant while levels of nickel oxide continued to increase (Dunnick et al. 1989).

Slow clearance of nickel oxide from the lungs was also observed in hamsters (Wehner and Craig 1972). Approximately 20% of the inhaled concentration of nickel oxide was retained in the lungs at the end of exposure for 2 days, 3 weeks, or 3 months. The retention was not dependent on the duration of exposure or exposure concentration. By 45 days after the last exposure to nickel oxide (2-day exposure), 45% of the initial lung burden was still present in the lungs (Wehner and Craig 1972). The nickel oxide used in this study was not further identified.

The clearance of nickel compounds from the lungs was studied following intratracheal injection (Carvalho and Ziemer 1982; Valentine and Fisher 1984). Nickel subsulfide (less soluble) was cleared from the lungs of mice in two phases: 38% of the given dose was cleared with a half-time of 1.2 days, and 42% was cleared with a half-time of 12.4 days. After 35 days, 10% of the dose remained in the lungs (Valentine and Fischer 1984). Soluble nickel chloride was cleared from the lungs much faster: 71% of the given dose was cleared from the lungs in 24 hours, and only 0.1% of the given dose remained in the lungs by day 21 (Carvalho and Ziemer 1982).

In a study that examined the effect of green nickel oxide and nickel sulfate on the clearance of nickel from the lungs, rats and mice were exposed 6 hours/day, 5 days/week, for up to 6 months and then given a single nose-only exposure to a ^{63}Ni-labeled compound (Benson et al. 1995a). Nickel sulfate at concentrations up to 0.11 mg nickel/m^3 had no effect on lung clearance of nickel sulfate. Nickel oxide exposure did reduce the lung clearance of nickel oxide. When measured 184 days after the single exposure, a 6-month exposure of rats to nickel oxide at 0, 0.49, and 1.96 mg nickel/m^3 was found to result in the retention of 18%, 33%, and 96% of the dose, respectively. In mice exposed to nickel oxide at 0, 0.98, or 3.93 mg/m^3 for 6 months, 4%, 20%, and 62%, respectively, of the dose was retained 214 days after the single exposure to radiolabelled compound.

2.3.2.2 Oral Exposure

An autopsy study of individuals not occupationally exposed to nickel has shown the highest concentrations of nickel μg/kg dry weight) in the lungs (174±94), followed by the thyroid (141±83), adrenals (132±84), kidney (62±43), heart (54±40), liver (50±31), brain (44±16), spleen (37±31), and pancreas (34±25) (Rezuke et al. 1987). In an autopsy study, median levels of 0.046, 0.084, and 0.33 μg nickel/g wet weight were found in the adrenal glands, colon, and skin,

respectively (Tipton and Cook 1963). The total amount of nickel found in the human body has been estimated as 6 mg or 86 μg/kg for a 70-kg person (Sumino et al. 1975).

Serum nickel levels peaked 2.5-3 hours after ingestion of nickel sulfate (Christensen and Lagesson 1981; Sunderman et al. 1989b). In workers who accidentally ingested water contaminated with nickel sulfate and nickel chloride, the mean serum half-time of nickel was 60 hours (Sunderman et al. 1988). This half-time decreased substantially (27 hours) when the workers were treated intravenously with fluids.

In animals, nickel was found primarily in the kidneys following both short-term and long-term oral exposure to various soluble nickel compounds (Ambrose et al. 1976; Borg and Tjalve 1989; Dieter et al. 1988; Ishimatsu et al. 1995; Jasim and Tjalve 1986a, 1986b; Oskarsson and Tjalve 1979; Whanger 1973). Substantial levels of nickel were also found in the liver, heart, lung, and fat (Ambrose et al. 1976; Dieter et al. 1988; Jasim and Tjalve 1986b; Schroeder et al. 1964; Whanger 1973) as well as in the peripheral nerve tissues and in the brain (Borg and Tjalve 1989; Jasim and Tjalve 1986a). Following a 2-year study in rats in which nickel levels were measured in bone, liver, kidney, and fat, Ambrose et al. (1976) concluded that there were no important storage sites for nickel. In control rats, bone nickel was 0.53 ppm in female rats and <0.096 ppm in male rats. An explanation for the difference in bone nickel between male and female rats was not provided. Nickel was found to cross the placenta, as indicated by increases in the levels of nickel in the fetuses of mice given nickel during gestation (Jasim and Tjalve 1986a; Schroeder et al. 1964).

In pregnant rats not exposed to nickel, maternal and fetal blood concentrations of nickel were 3.8 and 10.6 μg/L, respectively (Szakmary et al. 1995). Twenty-four hours after a single gavage dose of 5.4, 11.3, or 22.6 mg nickel/kg as nickel chloride was given to pregnant rats (gestation day 19), nickel levels in μg/L were 18.5, 90, and 91.5, respectively, in maternal blood, 14.5, 65.5 and 70.5, respectively, in fetal blood, and 16.5, 20, and 17, respectively, in amniotic fluid. This study showed that at higher doses, nickel reached a plateau in maternal and fetal blood, and that nickel concentrations in amniotic fluid were relatively well controlled in that they were similar at all three doses.

2.3.2.3 Dermal Exposure

No data were located regarding the distribution of nickel in humans after dermal exposure.

One hour after application of nickel to the shaved skin of guinea pigs, nickel had accumulated in keratinaceous areas and in hair sacs (Lloyd 1980). After 4 hours, nickel was found in the stratum comeum and stratum spinosum. Twenty-four hours after treatment of depilated skin in rabbits and guinea pigs with nickel-57, radioactivity was detected in the blood, kidneys, and liver with the greatest amounts found in the blood and kidneys (Norgaard 1957). Quantitative data were not provided. Concentrations of nickel in the liver were 2.4±0.l μg/g following 15 daily dermal treatments of guinea pigs with nickel sulfate at 100 mg nickel/kg/day, and 4.4±0.5 μg/g following 30 days of treatment with the same dose, compared to 0.2±0.01 ug/g before treatment (Mathur and Gupta 1994). In the kidneys, nickel levels in μg/g were 0.4±0.2 before treatment, 1.5±0.12 at 15 days, and 3.52±0.42 at 30 days.

2.3.2.4 Other Routes of Exposure

Several researchers have examined the distribution of nickel in pregnant and lactating rats following its injection (Dostal et al. 1989; Mas et al. 1986; Sunderman et al. 1978). Half-lives of nickel in whole blood following intraperitoneal treatment of pregnant and nonpregnant rats were similar (3.6-3.8 hours), while the half-life for nickel in fetal blood was 6.3 hours following treatment on gestation day 12 or 19 (Mas et al. 1986). Intramuscular injection of nickel chloride (12 mg nickel/ kg/day) into pregnant and nonpregnant rats resulted in a greater accumulation of nickel in the pituitary of pregnant rats (Sunder-man et al. 1978). Wet weight nickel concentrations in the pituitary were 0.13 μg/g in nonpregnant rats and 1.l and 0.91 μg/g in pregnant rats treated on gestation days 8 and 18, respectively. Following subcutaneous exposure of lactating rats to nickel chloride, Dostal et al. (1989) found that peak nickel concentrations in the milk were reached 12 hours after treatment. Relative to treatment with a single dose, four daily subcutaneous doses of nickel resulted in higher nickel concentrations in milk, while serum nickel levels were the same as following a single dose (Dostal et al. 1989). This study suggests that nickel can accumulate in the milk, which would result in exposure of the offspring.

Using whole-body autoradiography, Ilback et al. (1992, 1994) examined the distribution of an intravenous dose of nickel given to mice with and without coxsackie virus B3 infection. Virus infection changed nickel distribution, resulting in accumulation in the pancreas and the wall of the ventricular myocardium. The investigators suggested that the change in distribution may result from repair and immune mechanisms activated in response to the virus.

2.3.3 Metabolism

The extracellular metabolism of nickel consists of ligand exchange reactions (Sarkar 1984). In human serum, nickel binds to albumin, £-histidine, and α_2-macroglobulin. Binding in animals is similar. The principal binding locus of nickel to serum albumins is the histidine residue at the third position from the amino terminus in humans, rats, and bovines (Hendel and Sunderman 1972). Dogs do not have this binding locus, and most of the nickel (>85%) in dog serum was not bound to protein. A proposed transport model involves the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and $_L$-histidine. The low molecular weight $_L$-histidine nickel complex can then cross biological membranes (Sarkar 1984). In the serum, there is also a nonexchangeable pool of nickel tightly bound to nickeloplasmin, which is an α-macroglobulin (Sunderman 1986).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Absorbed nickel is excreted in the urine, regardless of the route of exposure (Angerer and Lehnert 1990; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). In nickel workers, an increase in urinary excretion was found from the beginning to the end of the shift, indicating a fraction that was rapidly eliminated. An increase in urinary excretion was also found as the workweek progressed, indicating a fraction that was excreted more slowly (Ghezzi et al. 1989; Tola et al. 1979). Nickel was also excreted in the feces of nickel workers, but this probably resulted from mucociliary clearance of nickel from the respiratory system to the gastrointestinal tract (Hassler et al. 1983). Among electrolysis and refinery workers exposed to soluble nickel compounds (nickel sulfate aerosols), nickel concentrations in the urine were 5.2-22.6 μg/L for those exposed to concentrations of 0.11-0.31 mg nickel/m^3, and 3.2-18 μg/L for

those exposed to 0.08-0.2 mg nickel/m^3 (Chashschin et al. 1994). Higher nickel levels were found in the urine of workers exposed to soluble nickel compounds, indicating that the soluble compounds are more readily absorbed than the less-soluble compounds (Bemacki et al. 1978; Totjussen and Andersen 1979). Although high levels of nickel were found in the urine of a man who died of adult respiratory distress syndrome 13 days after being exposed to a very high concentration of metallic nickel (Rendall et al. 1994), it is not clear if metallic nickel would be absorbed from healthy lungs.

In animals, the route of excretion following intratracheal administration of nickel depends on the solubility of the nickel compound. In rats given soluble nickel chloride or nickel sulfate, ≈70% of the given dose was excreted in the urine within 3 days (Carvalho and Zeimer 1982; Clary 1975; English et al. 1981; Medinsky et al. 1987). By day 21, 96.5% of the given dose of nickel chloride had been excreted in the urine (Carvalho and Zeimer 1982). Following intratracheal administration of less-soluble compounds (nickel oxide, nickel subsulfide), a greater fraction of the dose was excreted in the feces as a result of mucociliary clearance. Following administration of black nickel oxide to rats or nickel subsulfide to mice, approximately equal amounts of the initial dose were excreted in the urine and the feces (English et al. 1981; Valentine and Fischer 1984). A total of 90% of the initial dose of nickel subsulfide was excreted within 35 days (Valentine and Fischer 1984), and 60% of the initial dose of black nickel oxide was excreted within 90 days (English et al. 1981). This is consistent with nickel oxide being less soluble and not as rapidly absorbed as nickel subsulfide (English et al. 1981; Valentine and Fischer 1984).

2.3.4.2 Oral Exposure

In humans, most ingested nickel is excreted in the feces (Sunderman et al. 1989b). However, the nickel that is absorbed from the gastrointestinal tract is excreted in the urine. Nickel administered in the drinking water was absorbed much more readily than when administered in the food (27% absorption in water versus 0.7% absorption in food, respectively). By 4 days post-treatment, 26% of the dose given in water was excreted in the urine and 76% in the feces, and 2% of the dose given in food was excreted in the urine and 102% in the feces (Sunderman et al. 1989b). The elimination half-time for absorbed nickel averaged 28±9 hours (Sunderman et al. 1989b).

In animals, the majority of the ingested dose of nickel is excreted in the feces. One day after administration of nickel chloride in rats, 94-97% had been excreted in the feces and 3-6% had been excreted in the urine (Ho and Furst 1973). In dogs fed nickel sulfate in the diet for 2 years, only l-3% of the ingested nickel was excreted in the urine (Ambrose et al. 1976). Because dogs lack a major binding site in serum albumin that is found in humans (Hendel and Sunderman 1972), the relevance of dog data to humans is unclear.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of nickel in humans or animals after dermal exposure to nickel.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

2. HEALTH EFFECTS

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

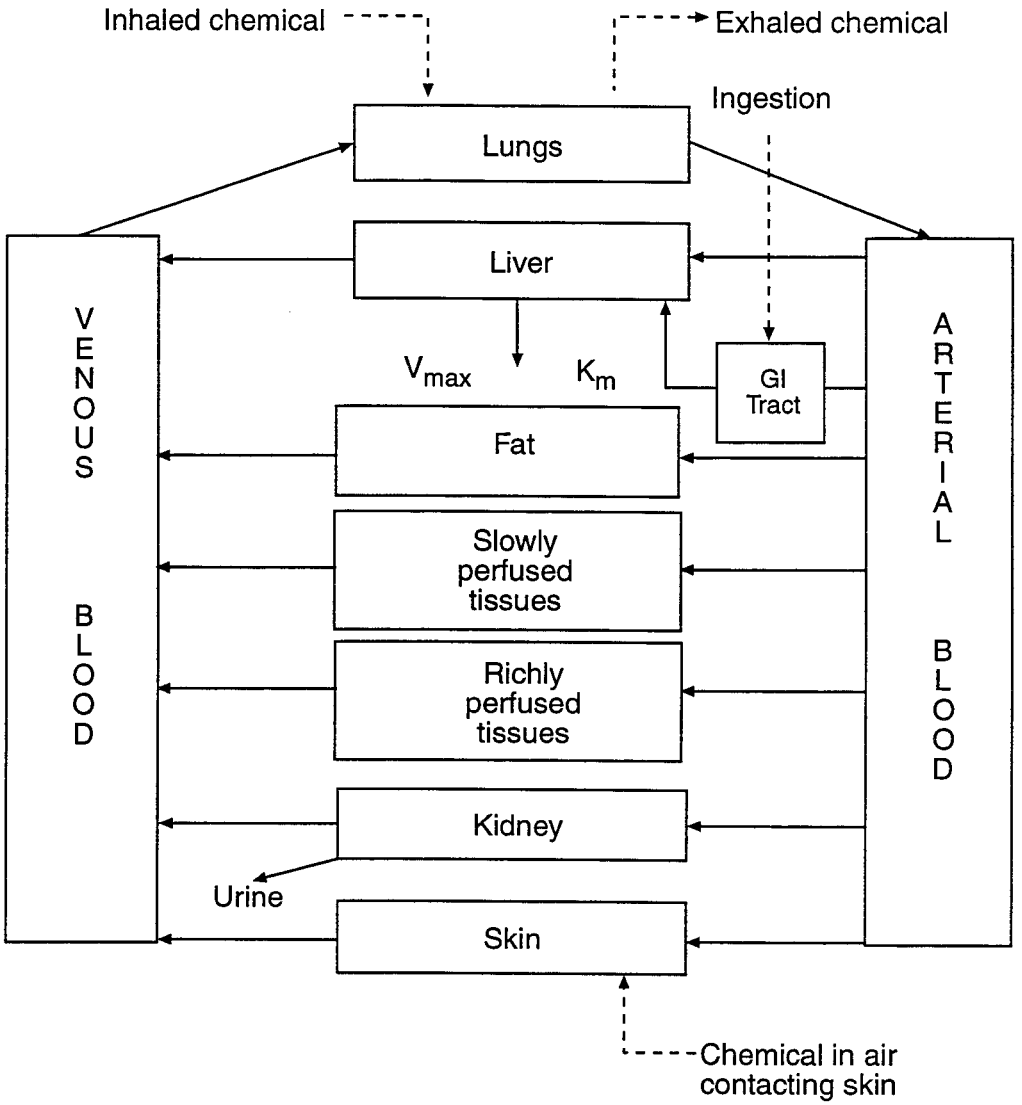
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

If PBPK models for nickel exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Sunderman et al. (1989b) have developed a model to predict nickel absorption, serum levels, and excretion following oral exposure to nickel in water and food. The model was developed based on two experiments in humans in which serum nickel levels and urinary and fecal excretion of nickel

Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

were monitored for 2 days before and 4 days after eight subjects were given an oral dose of nickel as nickel sulfate (12, 18, or 50 μg nickel/kg) in water (experiment 1) or in food (experiment 2). The data was then analyzed using a linear, compartmental, toxicokinetic model (Figure 2-4). Two inputs of nickel, the single oral dose, in which uptake was considered to be a first-order process, and the baseline dietary ingestion of nickel, in which uptake was considered to be a pseudo-zero order process, were included in the model. Parameters determined for the model from the two experiments are shown in Table 2-6. The only parameter that was significantly different between exposure in water and exposure in food was the fraction of nickel absorbed from the gastrointestinal tract. The absorption rate constant was not different at the different doses, but the investigators indicated that the observations do not exclude the possibility that nickel absorption from the gastrointestinal tract could be saturated at higher doses. At doses low enough to be in the deficiency range, the absorption rate and percentage absorbed are probably larger. The model has not yet been validated with additional human data.

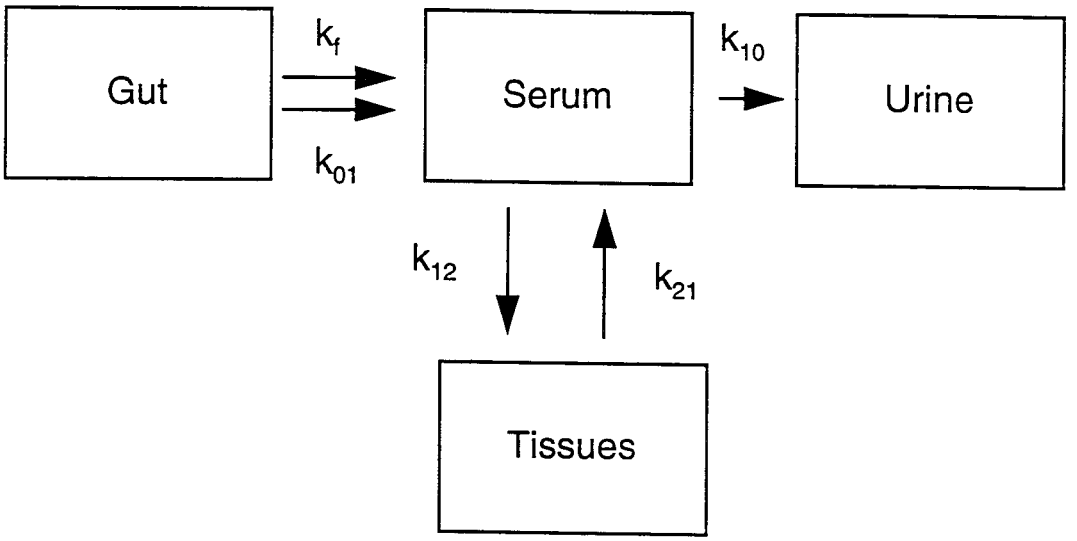
2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Nickel is thought to be absorbed from the gastrointestinal tract as a lipophilic low molecular weight compound (Kenney and McCoy 1992). The absorption of nickel from the gut is dependent on the various ligands and ions that are present. For example, food greatly decreases the absorption of nickel (Sunderman et al. 1989b). *In vitro* studies using segments of ileum and jejunum from the rat indicate that nickel is actively absorbed in the jejunum but may cross the ileum by passive diffusion (Tallkvist and Tjalve 1994).

In the plasma nickel is transported by binding to albumin, and ultrafiltrable ligands which include small polypeptides and amino acids, for example, histidine (Sunderman and Oskarsson 1991). The nickel binding site on albumin consists of the terminal amino group, the first two peptide nitrogen atoms at the *N*-terminus, and the imidazole nitrogen of the histidine at the third position from the *N*-terminus. Nickel competes with copper for this albumin binding site. In the plasma nickel is also found bound to nickeloplasmin, an a-macroglobulin, but the nickel associated with nickeloplasmin is not readily exchangeable, and this protein is not thought to play a role in the

FIGURE 2-4. Diagram of the Compartmental Model of Nickel Metabolism*



*Modified from Sunderman et al. 1989b

k_f = zero-order rate constant for fractional absorption of dietary nickel
k_{01} = first-order rate constant for intestinal absorption of nickel from oral $NiSO_4$
k_{12} = first order rate constant for nickel transfer from serum to tissues
k_{21} = first-order rate constant for nickel transfer from tissue to serum
k_{10} = first-order rate constant for nickel excretion in urine

TABLE 2-6. Kinetic Parameters of Nickel Absorption, Distribution, and Elimination in Humans[a]

Parameters (symbols and units)	Experiment 1 (nickel sulfate in water)	Experiment 2 (nickel sulfate in food)
Mass fraction of nickel dose absorbed from the gastrointestinal tract (F, %)	27 ± 17	0.7 ± 0.4[b]
Rate constant for alimentary absorption of nickel from the nickel dose (k_{01}, $hour^{-1}$)	0.28 ± 0.11	0.33 ± 0.24
Rate constant for alimentary absorption of dietary nickel intake (k_f, µg/hour)	0.092 ± 0.051	0.105 ± 0.036
Rate constant for nickel transfer from serum to tissues (k_{12}, $hour^{-1}$)	0.38 ± 0.17	0.37 ± 0.34
Rate constant for nickel transfer from tissue to serum (k_{21}, $hour^{-1}$)	0.08 ± 0.03	___[c]
Rate constant for urinary elimination of nickel (k_{10}, $hour^{-1}$)	0.21 ± 0.05	0.15 ± 0.11
Rate clearance of nickel (C_{Ni}, mL/minute/1.73 mg/m^2)	8.3 ± 2.0	5.8 ± 4.3
Rate clearance of creatinine ($C_{creatinine}$, mL/minute/1.73 mg/m^2)	97 ± 9	93 ± 15
Nickel clearance as % of creatinine clearance ($C_{Ni}/C_{creatinine}$, ×100)	8.5 ± 1.8	6.3 ± 4.6

[a]Data (mean ± standard deviation) from Sunderman et al. 1989b

[b]$p<0.001$ relative to exposure in food computed by analysis of variance

[c]No value was determined because of the small mass of nickel absorbed from the gastrointestinal tract and transferred from the serum into the tissues.

transport of nickel (Sunderman and Oskarsson 1991). At physiological levels, no tissue significantly accumulates orally administered nickel (Nielsen 1990).

Nickel that is absorbed is excreted primarily in the urine. In the urine, nickel is primarily associated with low molecular weight complexes that have free amino acids as indicated by the ninhydrin reaction (Sunderman and Oskarsson 1991). In humans nickel is also eliminated in hair, skin, milk, and sweat.

The physiological role of nickel in animals and humans has not yet been identified. The most likely roles are as cofactors in metalloenzymes or metalloproteins, or as a cofactor that facilitates the intestinal absorption of iron (Fe^{3+} ion) (Nielsen 1982). Support for a role of nickel in enzymes comes from the identification of nickel-containing enzymes in plants and microorganisms. The types of nickel-containing enzymes that have been identified are urease, hydrogenase, methylcoenzyme M reductase, and carbon monoxide dehydrogenase (Nielsen 1990). Nickel may also have a role in endocrine gland function as suggested by its effect on prolactin levels.

2.4.2 Mechanisms of Toxicity

The mechanism of respiratory effects following lung exposure of rabbits to metallic nickel or nickel chloride has been examined (Johansson and Camner 1986; Johansson et al. 1980, 1981, 1983, 1987, 1988a, 1989). In these studies, an accumulation of macrophages and granular material (primarily phospholipids) in the alveoli and an increase in volume density of alveolar type II cells were observed. The type II cells contained large amounts of lamellar bodies. The macrophage effects may have been a result of the high amounts of surfactant produced by the hyperplastic type II cells. Similar results were found following exposure to metallic nickel and nickel chloride, indicating that nickel ions apparently had a direct effect on type II cells (Johansson and Camner 1986). At the end of 6 months, all of the rabbits had foci of pneumonia, indicating an increased susceptibility to infection (Johansson et al. 1981). This may have been a result of the decreased function of the alveolar macrophages.

Injection studies have shown that nickel can decrease body temperature (Gordon 1989; Gordon et al. 1989; Hopfer and Sunder-man 1988; Watanabe et al. 1990). Because nickel also disturbs the circadian rhythm of temperature regulation, this decrease is thought to result from an effect on the

central nervous system. It has been speculated that nickel may mimic the effect of calcium on the hypothalamic thermoregulatory center resulting in hypothermia (Hopfer and Sunderman 1988).

The substitution of nickel for other essential elements may also contribute to the adverse effects of nickel. Nickel can replace magnesium in certain steps in the activation of complement (McCoy ant Kenney 1992). For example, nickel greatly increased the half-life and stability of the C3b, Bb enzyme which amplifies activation of the complement pathway. Nickel has also been shown to activate calcineurin, a phosphatase that binds zinc and iron, and which is usually activated by manganese (Kenney and McCoy 1992).

There is some evidence that nickel may have a role in the release of prolactin from the pituitary. *In vitro* studies have shown that nickel could directly inhibit the release of prolactin by the pituitary, and it has been suggested that nickel may be part of a prolactin inhibiting factor (LaBella et al. 1973). Intravenous exposure to nickel chloride has been shown to reduce serum levels of prolactin in male rats that were pretreated with chlorpromazine, which itself produces hyperprolactinemia (LaBella et al. 1973). The effect was not observed in rats that had not been pretreated with chlorpromazine. Nickel has also been shown to accumulate more in the pituitaries of pregnant rats than nonpregnant rats (Sunderman et al. 1978), suggesting that a toxicological effect through prolactin may only be manifest during maximum prolactin production. A subcutaneous injection study has also shown that nickel can change the quality of the milk produced, resulting in increased milk solids (42%) and lipids (1l0%), and decreased protein (29%) and lactose (61%) (Dostal et al. 1989). Because these changes were noted in comparison to pairfed rats, they were not considered to be a result of changes in food intake. An effect on prolactin would help explain the reproductive effects (maternal deaths during delivery, perinatal deaths) observed in multigeneration studies (Ambrose et al. 1976; RTI 1988a, 1988b; Smith et al. 1993) and the lack of dose response observed in these studies. The reproductive effects may be a result of physiological changes induced by nickel through changes in prolactin levels rather than a direct effect of nickel.

Costa (1989) reviewed potential mechanisms of nickel carcinogenesis. Soluble nickel compounds, although genotoxic *in vitro*, are rapidly cleared *in vivo* and therefore are not carcinogenic *in vivo* (Kasprzak et al. 1983; Sunderman and Maenza 1976). Particle solubility is not the only property that determines the genotoxic potential of nickel compounds; the physical form of the nickel

particles is also important. Costa and Mollenhauer (1980) found that crystalline but not amorphous nickel subsulfide transformed Syrian hamster embryo cells *in vitro* and was phagocytized by cells that were transformed. The crystalline particles had a greater negative charge than the amorphous particles that allowed the crystalline particles to be phagocytized. Once inside the phagosomes, the crystalline nickel subsulfide is dissolved through acidification of vacuoles by lysozymes. The nickel II ions released in this process are then delivered to the nucleus where they interact with DNA or DNA protein complexes (Costa 1995). In contrast, soluble nickel compounds are taken into the cytosol and are not delivered to the nucleus, which prevents the interaction of nickel ions with DNA.

Most DNA damage induced by nickel ions is thought to occur during the late S phase of the cell cycle when heterochromatic DNA is replicating (Costa 1989). Evidence suggests that nickel may alter gene expression by enhanced DNA methylation and compaction (Lee et al. 1995). Methylation of DNA may result in critical genes becoming incorporated into heterochromatin where they can no longer be expressed (Costa 1995). There is also evidence that nickel ions inhibit DNA repair (Hartwig et al. 1994). Nickel enhances the genotoxicity of ultraviolet light, x-rays, *cis-* and *trans*-platinum, and mitomycin C. *In vitro* studies in HeLa cells suggest that nickel inhibits the incision step in excision repair (Hartwig et al. 1994), while studies using Chinese hamster ovary cells, suggest that nickel inhibits the ligation step of excision repair (Lee-Chen et al. 1994). The underlying mechanism of how nickel affects DNA repair is unclear. Sunderman and Barber (1988), Sunderman (1989b), and Hartwig et al. (1994) suggest that nickel ions may compete with zinc ions for binding to zinc-finger DNA binding proteins, resulting in structural changes in DNA that prevent repair enzymes from binding. Nickel may also directly interact with enzymes required for DNA repair (Hartwig et al. 1994).

2.4.3 Animal-to-Human Extrapolations

Serum albumin found in dogs lacks the histidine residue at the third position from the amino terminus (Hendel and Sunderman 1972). Therefore, dogs would not be a good model for the disposition of nickel in humans.

Extrapolation of animal data concerning the inhalation of nickel particles requires the use of a factor to estimate the deposition of particles of a certain size in human lungs relative to the lungs

of animals (EPA 1990a). Particles of different sizes deposit in different regions of the respiratory tract in laboratory animals and humans. This difference is a result of several factors including a more convoluted nasal turbinate system and smaller airway size in rats and mice which are obligate nose breathers. Therefore, particles are more likely to deposit in the nasal passages in rats and mice compared to humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Nickel is a natural element of the earth's crust; therefore, people are constantly exposed to small amounts in food, water, and soil, and even smaller amounts in air. Although a nickel deficiency syndrome has not been identified in humans, nickel deficiency has been induced in several species of animals (e.g., rats, chicks, cows, goats), indicating that nickel is essential in these species (Nielsen 1982; Nielsen and Ollerich 1974; Nielsen and Sandstead 1974; Nielsen et al. 1975). Nickel deficiency is manifested primarily in the liver; effects include abnormal morphology, oxidative metabolism, and lipid levels. A decrease in growth and hematocrit have also been noted. The function of nickel is not known, but it has been suggested that nickel acts as a bioligand cofactor that facilitates the gastrointestinal absorption of the ferric ion (Nielsen 1982). Nickel has been found to affect the absorption of iron but only when the iron was given as ferric sulfate (see Section 2.6) (Nielsen 1980; Nielsen et al. 1980, 1984). No effect was found when iron was given as a 60% ferric/40% ferrous sulfate mixture. Nielsen (1982) suggested that nickel is necessary for the formation or integrity of a molecule involved in the absorption of the ferric ion. Nickel may also have a role in normal endocrine function affecting prolactin levels (Kenney and McCoy 1992). The nickel requirement has been estimated to be 50 μg/kg of diet for rats and chicks and >l00 μg/kg of diet for cows and goats (Nielsen 1982). The higher level in cows and goats may be due to the use of nickel by rumen bacteria. Based on animal data, it is suggested that a dietary level of 50 μg/kg of diet would be reasonable for humans. Because the average oral intake of nickel in the United States is about 150-568 μg/day (0.002-0.0024 mg/kg/day; 70-kg person), nickel deficiency should not be a concern for the general public.

In humans, the most prevalent effect of nickel is nickel dermatitis in nickel-sensitive individuals. Sensitization is most likely to occur following prolonged dermal contact with nickel-containing materials including jewelry. Sensitization has also occurred following occupational exposure to nickel. Sensitized individuals may then react to low doses of nickel following inhalation, oral, and

dermal exposure. A few sensitive individuals develop asthma following exposure to nickel. Although oral exposure to nickel may cause a reaction in some sensitive individuals, continued oral exposure to nickel may desensitize some individuals, and it may also prevent some people from becoming sensitive to nickel.

Following inhalation exposure of humans to nickel particles, primarily as nickel oxides and nickel refinery dust, the respiratory system is the primary target. Effects noted included chronic bronchitis, emphysema, reduced vital capacity, and cancers of the lungs and nasal sinus. These effects occurred at concentrations much higher than those found in the environment. Oral exposure of humans to levels much greater than background has resulted in death (due to cardiac arrest), gastrointestinal effects (nausea, cramps, diarrhea, vomiting), hematological effects (increase in reticulocytes), hepatic effects (increase in serum bilirubin), renal effects (albuminuria), and neurological effects (giddiness, weariness).

In animals, effects similar to those observed in humans were reported for all routes of exposure. Following inhalation exposure, the respiratory tract was the primary target of toxicity in animals. Both carcinogenic and noncarcinogenic effects were observed in the respiratory tract. Although soluble nickel compounds are more toxic to the respiratory tract than less soluble compounds, they are readily cleared from the lungs. In contrast, less-soluble compounds which are only slowly cleared from the lungs are less toxic than soluble nickels compounds but were carcinogenic in animal studies.

Following high oral exposure to nickel, effects in animals included death, respiratory effects, gastrointestinal effects, hematological effects, hepatic effects, renal effects, decreased body weight, reduced food and water intake, immunological effects, neurological effects, and reproductive effects. Carcinogenic effects have not been observed following oral nickel exposure. Nickel sensitivity and dermal effects have been observed after dermal exposure to nickel.

2. HEALTH EFFECTS

Minimal Risk Levels for Nickel

Inhalation MRLs

- An MRL of $2x10^{-4}$ mg/m^3 has been derived for chronic-duration inhalation exposure to nickel.

This MRL is based on a 2-year study of nickel sulfate in rats in which chronic active inflammation was observed at ≥0.06 mg nickel/m3 (NTP 1996c). The inflammation was described as multifocal, minimal to mild accumulations of macrophages, neutrophils, and cell debris within alveolar spaces. The prevalence of fibrosis was also significantly increased at ≥0.06 mg nickel/m^3. Based on the NOAEL of 0.03 mg/m3, the MFX was calculated as described in the footnote to Table 2-l. In mice exposed to nickel sulfate for 2 years, inflammatory lesions in the lungs were observed at 20.06 mg nickel/m3 (NTP 1996c). Similar studies in which F344 rats and $B6C3F_1$ mice were exposed to nickel subsulfide and nickel oxide confirm that the lungs are the principal target of nickel following inhalation exposure (NTP 1996a, 1996b). This MRL, based on nickel sulfate, is most applicable to soluble nickel compounds that are less likely to be found in the environment.

Data are insufficient for derivation of an acute inhalation MRL for nickel because a less-serious LOAEL was not identified for the most toxic nickel compound, nickel sulfate. In an acute study (exposure 12/16 days), the lowest concentration of nickel sulfate studied (0.8 mg nickel/m^3) resulted in labored breathing, pneumonia, degeneration of the respiratory epithelium, atrophy of the olfactory epithelium, and a 28% decrease in body weight gain (Benson et al. 1988; Dunnick et al. 1988; NTP 1996c).

In an intermediate-duration inhalation study of nickel sulfate in rats (Dunnick et al. 1989; NTP 1996c), alveolar macrophage hyperplasia was observed at all concentrations (0, 0.03, 0.06, 0.11, 0.22, and 0.44 mg nickel/m^3), and chronic active inflammation of the lungs and olfactory epithelial atrophy were noted at 0.6 mg/m^3. Macrophage hyperplasia tends to be an inconsistent or perhaps reversible effect that showed an increase after 7 months of exposure but not at 2 years in the chronic study. In addition to being a minimal or reversible effect, alveolar macrophage hyperplasia can be attributed to the physical stimulus of particulate treatment and is not necessarily specific for nickel. Therefore use of 0.03 mg/m^3 as a LOAEL for macrophage hyperplasia to derive an intermediate MRL is questionable. Because the NOAEL identified in the chronic study

(0.03 mg/m^3) is at the level of a minimal LOAEL in the intermediate-duration study, the chronic MRL should be protective of both chronic- and intermediate-duration exposures.

Oral MRLs

No oral MRLs were derived. Following a single dose of 0.05 mg nickel/kg in drinking water, a male volunteer developed left homonymous hemianopsia (Sunderman et al. 1989b). Nickel, following oral exposure, can also cause dermal reactions in sensitive people (Burrows et al. 1981; Christensen and Moller 1975; Cronin et al. 1980; Gawkrodger et al. 1986; Kaaber et al. 1978; Veien et al. 1987). The lowest single dose resulting in dermatitis was 0.009 mg/kg/day (Cronin et al. 1980). Because of concern about protecting sensitive individuals, and because application of uncertainty factors to the LOAEL would bring the dose below normal dietary intake (about 0.002 mg/kg/day), oral MRLs were not derived.

Death. Inhalation exposure to very high concentrations of small particle size metallic nickel has resulted in the death of one subject from adult respiratory distress syndrome (Rendall et al. 1994). Several studies have found a relationship between increased mortality and nonmalignant respiratory disease and nasal and lung cancers in nickel-exposed workers (Cornell and Landis 1984; Polednak 1981). The increase in deaths in the Polednak (1981) study was not statistically significant. Other occupational studies have not reported increased mortality due to respiratory disease (Cox et al. 1981; Cragle et al. 1984; Enterline and Marsh 1982; Redmond 1984; Shannon et al. 1984a, 1984b, 1991). A child who accidentally ingested nickel sulfate died from cardiac arrest (Daldrup et al. 1983).

Nickel can be lethal to animals after inhalation or oral exposure. In animal studies, soluble nickel compounds (nickel sulfate, nickel chloride, nickel acetate) were more toxic than the less-soluble nickel compounds (nickel oxide, nickel subsulfide). Specific causes of death were not reported following either route of exposure, but clinical signs observed prior to death from oral exposure included lethargy, ataxia, irregular breathing, cool body temperature, salivation, squinting, and loose stools (Dieter et al. 1988). An increase in deaths resulting from complications of pregnancy was found in rats during a two-generation oral exposure study, indicating that the animals were more susceptible during pregnancy (RTI 1988a, 1988b). The results of the RTI (1988a, 1988b) study are questionable, however, because decreases in food and water intake were observed in the exposed

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dams, and temperatures were transiently increased as much as 10°F. Parenteral studies in rats and mice provide further evidence that late gestation pregnancy may enhance susceptibility to nickel. The LD_{50} of nickel in rats given as nickel chloride by intramuscular injection was 22 mg/kg on gestation day 8, and 16 mg/kg on gestation day 18 (Sunderman et al. 1978). No pregnant mice died when given a single intraperitoneal injection of 5.7 mg nickel/kg as nickel chloride on gestation day 7 or 8, while 2/10, 2/7, and 2/7 died following treatment with the same dose on gestation days 9, 10, and 11, respectively (Lu et al. 1979). The apparent pregnancy-enhanced toxicity of nickel may also be a result of increasing fetal body weights accounting for a greater proportion of the combined maternal and fetal body weights so that the dam is actually receiving a larger dose when treated later in gestation.

Both the human and animal data indicate that it is unlikely that exposure to nickel in the environment or at hazardous waste sites will result in human deaths. Accidental exposure to high levels of nickel, however, may cause death.

Systemic Effects

Respiratory Effects. Effects on the respiratory system of welders (Kilbum et al. 1990; Polednak 1981) and foundry workers (Cornell and Landis 1984) exposed to nickel included chronic bronchitis, emphysema (Cornell and Landis 1984; Polednak 1981), and reduced vital capacity (Kilbum et al. 1990). The workers, however, were also exposed to other toxic metals including uranium, iron, lead, and chromium. Therefore, it cannot be concluded that nickel was the sole causative agent. Based on mortality data, other studies have not reported increases in nonmalignant respiratory diseases (Cox et al. 1981; Cragle et al. 1984; Redmond 1984; Shannon et al. 1984a, 1984b, 1991). Advances in technology and improvements in industrial hygiene over the years have reduced the likelihood of respiratory effects in occupationally exposed individuals. In nickelsensitive individuals, inhalation exposure to nickel can result in asthma (Dolovich et al. 1984; Novey et al. 1983). No respiratory effects in humans were observed after oral or dermal exposure to nickel.

Respiratory effects in animals after inhalation exposure to nickel were similar to those observed in humans. The effects included increased lung weights, emphysema, chronic inflammation, fibrosis, macrophage hyperplasia, interstitial infiltrates, and atrophy of the olfactory epithelium (Benson et al.

1989; Dunnick et al. 1989; NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974). Respiratory effects in animals were observed after inhalation exposure to both soluble and less-soluble nickel compounds. The severity of the inflammatory response depended on the solubility of the nickel compound and not on the lung burden of nickel; less-soluble nickel oxide had the lowest toxicity and the highest lung burden. The studies indicate that the toxicity ranking was nickel sulfate > nickel subsulfide > nickel oxide (Benson et al. 1987, 1988, 1989; Dunnick et al. 1988, 1989; NIP 1996a, 1996b, 1996c).

Based on both the human and animal data, it is unlikely that exposure to nickel in the environment or at hazardous waste sites will result in respiratory effects. Occupational exposure to high levels of nickel, however, may result in serious respiratory effects.

Cardiovascular Effects. A 2-year-old child died from cardiac arrest following accidental ingestion of nickel sulfate (Daldrup et al. 1983). No increases in numbers of deaths from cardiovascular diseases were reported in nickel workers (Cornell and Landis 1984; Cox et al. 1981; Cragle et al. 1984). Changes in heart weight were observed in animals after longer term oral exposure to nickel, but the significance of these effects is not known (Ambrose et al. 1976; American Biogenics Corporation 1988). Parenteral studies in dogs indicate that exposure to 0.01-10 mg nickel/kg/day results in coronary vasoconstriction and myocardial depression (Ligeti et al. 1980; Rubanyi et al. 1984). Because these studies were completed in dogs, in which plasma binding of nickel differs from humans, the relevance of these studies to humans is unclear. The effects on the cardiovascular system may be a direct effect of nickel ions acting in a manner similar to that of calcium ions. It is not known whether exposure to nickel may exacerbate ischemic heart disease or increase the risk of myocardial infarction in patients with heart disease (EPA 1986a), but exposure to nickel at environmental levels encountered at hazardous waste sites is unlikely to result in cardiovascular effects.

Gastrointestinal Effects. Gastrointestinal effects including nausea, cramps, diarrhea, and vomiting were reported by workers exposed to high levels of nickel in water from a contaminated water fountain (Sunderman et al. 1988). The water was also contaminated with boric acid, and the possible contribution of boric acid to the observed effects is not known; however, the effects are not likely to be a result of boric acid levels on their own. Gastrointestinal effects were also observed in rats that died following oral exposure to high doses of nickel. These effects included

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ulcerative gastritis and enteritis in rats treated by gavage with nickel chloride (American Biogenics Corporation 1988). No gastrointestinal effects were found in rats or dogs chronically exposed to nickel sulfate in the diet (Ambrose et al. 1976). The difference in results in these two studies may be due to the administration of different nickel compounds or the routes of exposure (gavage versus diet). No gastrointestinal effects in humans or animals were observed after inhalation exposure to nickel. The results of these studies are indicative of an irritating effect of high doses on the gastrointestinal mucosa. It is unlikely that chronic, low-level exposure to nickel in food and drinking water would result in gastrointestinal irritation.

Hematological Effects. A transient increase in blood reticulocytes was observed in workers exposed to nickel in water from a contaminated water fountain (Sunderman et al. 1988). The water was also contaminated with boric acid, and the contribution of boric acid to this effect is not known. Inconsistent effects on hematocrit values were found in rats following inhalation exposure (Weischer et al. 1980). A reversible decrease in hemoglobin and increases in leukocyte counts were observed in rats after oral exposure to nickel (American Biogenics Corporation 1988; Whanger 1973). Intrarenal injection of nickel subsulfide in animals resulted in erythrocytosis (Hopfer and Sunder-man 1978; Hopfer et al. 1984). Studies indicate that the erythrocytosis is mediated by an increased renal production of erythropoietin. Erythropoietin is a protein produced by the kidney, which enhances erythropoiesis by stimulating the formation of proerythrocytes and the release of reticulocytes from the bone marrow. Overall, the results indicate that nickel exposure results in hematological effects in both humans and animals at high levels of exposure. It is unlikely, however, that exposure to levels of nickel in the environment or levels found at hazardous waste sites would result in hematological effects.

Musculoskeletal Effects. Muscular pain was reported by one worker exposed to nickel in drinking water from a contaminated drinking fountain (Sunderman et al. 1988). The cause of the muscular pain was not reported in the study, and the significance of this effect is not known.

Musculoskeletal effects were not observed in animals exposed to nickel by any route (Ambrose et al. 1976; Benson et al. 1987, 1988; Dunnick et al. 1988). It is unlikely that exposure of humans to nickel in the environment or at hazardous waste sites would result in adverse musculoskeletal effects.

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Hepatic Effects. A transient increase in serum bilirubin levels was observed in workers exposed to nickel in drinking water from a contaminated water fountain (Sunderman et al. 1988). Liver weight changes were found in animals following both inhalation and oral exposure to nickel (Ambrose et al. 1976; American Biogenics Corporation 1988; Dieter et al. 1988; Weischer et al. 1980). Subcutaneous injection of nickel chloride resulted in acute hepatic toxicity characterized by enhanced lipid peroxidation, microvesicular steatosis of hepatocytes, and increased activities of serum aspartate aminotransferase and alanine aminotransferase (Donskoy et al. 1986). A subcutaneous injection of nickel chloride given to mice was found to significantly decrease the hepatic activity of ethyl morphine *N*-demethylase, aminopyrine *N*-demethylase, and aniline 4-hydroxylase (Iscan et al. 1995). Cytochrome P-450, cytochrome b_5, and heme levels were also reduced. The significance of the liver weight changes is unclear, but the hepatotoxicity following parenteral administration indicates that nickel can be a hepatotoxin in animals. It is unlikely, however, that exposure of humans to nickel in the environment or at hazardous waste sites will result in hepatic effects.

Renal Effects. A transient increase in urine albumin was found in workers exposed to nickel in drinking water from a contaminated drinking fountain (Sunderman et al. 1988). In workers occupationally exposed to nickel, a significant association was found between nickelemia and increased levels of urinary β_2-microglobulin (Sunderman and Horak 1981). In another study, markers of tubular dysfunction (urinary lysozyme, NAG, β_2-microglobulin, retinol binding protein) were significantly increased in workers occupationally exposed to soluble nickel compounds (Vyskocil et al. 1994a). Markers of glomerular function (urinary albumin, transferrin) were not affected.

In a study in which rats were treated with nickel sulfate in the drinking water, an increase in albumin was observed, but markers of tubular function (urinary lactate dehydrogenase, NAG, β_2-microglobulin) were not affected (Vyskocil et al. 1994b). Renal tubular damage (damage to the convoluted tubules) and possible protein loss were observed in animals after oral exposure to nickel (Dieter et al. 1988). Changes in kidney weight were also observed in animals after inhalation or oral exposure to nickel (Ambrose et al. 1976; Weischer et al. 1980). Parenteral studies in animals indicate that nickel is a nephrotoxin, with the glomerular epithelium being the target of nickel toxicity (Foulkes and Blanck 1984; Gitlitz et al. 1975).

Thus, animal data indicate that nickel can damage glomerular function and cause renal tubular damage, while data in humans indicate that occupational exposure to nickel can result in tubular damage without affecting glomerular function. It is unlikely that environmental exposure or exposure at hazardous waste sites will result in renal effects.

Endocrine Effects. Endocrine effects have not been reported in humans exposed to nickel by any route. Adrenal medulla hyperplasia was observed in rats following chronic inhalation exposure to nickel oxide (NTP 1996a). Other microscopic examinations of endocrine organs following inhalation and oral exposure of animals to nickel have not revealed any changes in endocrine glands (Benson et al. 1987; Dunnick et al. 1988; NTP 1996b, 1996c; Ottolenghi et al. 1974). Observations of hyperglycemia and reproductive effects in animals suggest that subtle effects on endocrine glands may be occurring in animals exposed to high levels of nickel. Parenteral studies also suggest that nickel can affect endocrine gland function.

Hyperglycemia has been observed in animals after oral exposure (Weischer et al. 1980) and parenteral exposure (Clary 1975; Horak and Sunderman 1975a, 1975b; Kadota and Kurita 1955) to nickel. Increased levels of plasma glucagon were also observed in rats receiving an intraperitoneal injection of nickel chloride (Horak and Sunderman 1975a). Adrenalectomy or hypophysectomy partially inhibited the nickel-induced hyperglycemia (Horak and Sunderman 1975b), suggesting that a mechanism that does not involve the adrenal gland may also be involved. Damage to the pancreatic islet cells was also observed in rabbits following a single intravenous injection of nickel chloride. There was a marked decrease in the number of alpha cells (which secrete glucagon) and cellular damage to the beta cells (which secrete insulin) (Kadota and Kurita 1955). Clary (1975) reported an increase in glucose and a decrease in insulin in rats given an intratracheal injection of nickel chloride. Alvarez et al. (1993) found that the hyperglycemic response of rats to a single intraperitoneal dose of nickel chloride (4 mg nickel/kg) could be prevented by α-adrenergic antagonists but not by β-adrenergic antagonists. Because the hyperglycemic response to nickel cannot be completely blocked by adrenalectomy, these investigators suggest that catecholamine released by the central nervous system also plays a role in the reduction of insulin levels that leads to the hyperglycemic response to nickel.

As discussed in Section 2.4, there is some evidence that nickel may affect the release of prolactin from the pituitary. In a study limited by decreased water and food intake and increased

temperatures, oral exposure of rats resulted in increased pituitary weights in male but not female rats (RTI 1986, 1988a, 1988b). However, decreased prolactin levels were observed in female rats treated with nickel chloride in the drinking water throughout the breeding and lactation of two litters (Smith et al. 1993). Intravenous exposure to nickel chloride has been shown to reduce serum levels of prolactin in male rats which were pretreated with chlorpromazine, which itself produces hyperprolactinemia (LaBella et al. 1973). The effect was not observed in rats that had not been pretreated with chlorpromazine. Nickel has also been shown to accumulate in the pituitaries in pregnant rats more than in nonpregnant rats (Sunderman et al. 1978), suggesting that a toxicological effect through prolactin may only be manifest during maximum prolactin production.

Studies identifying endocrine effects in animals do not clearly identify a dose-response relationship. In addition, it has been suggested that nickel has a physiological role in endocrine gland function, affecting prolactin levels (Kenney and McCoy 1992). Therefore, further research is required to differentiate levels of nickel required by humans for normal endocrine function, compared to levels that may impair endocrine function leading to adverse effects. It is unlikely that environmental exposure or exposure to nickel at hazardous waste sites will result in endocrine effects.

Dermal Effects. Contact dermatitis, resulting from dermal exposure to nickel, is the most prevalent effect of nickel in the general population. Primary nickel sensitization occurs when metal objects are in contact with the skin for hours and nickel is released in response to friction and sweating. Metallic nickel and many nickel alloys release soluble nickel under humid conditions. The salts and amino acids in human sweat increase the corrosive action of water. Nickel must be in a soluble state to pass through the horny layer of skin. Several population studies have estimated that l-5% of males and 7-14% of females are contact sensitized to nickel (Menne and Maibach 1989; Menne et al. 1989). In nonoccupational exposures, the primary cause of nickel allergy is the wearing of jewelry containing nickel (Menne and Maibach 1989; Menne et al. 1989; Wilkinson and Wilkinson 1989). Ear piercing has also been associated with nickel sensitivity (Larsson-Stymne and Widstrom 1985; van Hoogstraten et al. 1994). Occupational sources of nickel contact sensitization have also been reported. Nickel plating and electroforming, nickel refining, and hairdressing are some of the occupations associated with nickel contact dermatitis (Fischer 1989). Improved hygiene practices have resulted in a decrease in the prevalence of nickel sensitivity in workers. Once an individual is sensitized, much smaller amounts of nickel may elicit a reaction.

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The prevalence of nickel dermatitis among persons with contact dermatitis has been reported in several surveys. In a patch test study, 11-12% of the patients were sensitive to nickel sulfate applied as a 2.5% solution (Nethercott and Holness 1990; North American Contact Dermatitis Group 1973). The results indicate that blacks have a higher incidence of positive reactions than whites, and that women in either racial group have a higher incidence of reactions than men. The incidence of reactions in women is probably higher because they wear more jewelry than men. The result from a mouse study (Siller and Seymour 1994) showing a difference between males and females in the sensitization response suggests that differences in exposure may not completely account for the difference in nickel sensitivity between women and men. Nickel sensitivity has also been observed in pediatric populations (Ho and Johnston 1986; Veien et al. 1982). In a survey of subjects more representative of the general population, it was concluded that ≈5% of the general population is sensitive to nickel and that females are more sensitive than males (Prystowsky et al. 1979). Cross-sensitivity of nickel and other metals (e.g., cobalt) has also been reported (Veien et al. 1987).

Studies in sensitized individuals found that allergic dermatitis can occur following a single oral dose of ≈0.009 mg/kg (Cronin et al. 1980). However, other studies have demonstrated that the elicitation of allergic dermatitis requires a single oral dose of ≈0.04 mg/kg or higher (Burrows et al. 1981; Gawkrodger et al. 1986; Kaaber et al. 1978). Menne and Maibach (1987) concluded that "only a minor number of nickel sensitive patients react to oral doses below 0.02 mg/kg, but most will react at doses of 0.08 mg/kg." The interpretation of results in humans is confounded by study limitations such as lack of a double-blind study protocol and the finding of placebo effects (dermatitis after administration of placebo). Intermediate-duration studies suggest that longer term oral exposure can be tolerated by some nickel-sensitive individuals and may even serve to desensitize some individuals (Jordan and King 1979; Santucci et al. 1994; Sjovall et al. 1987). Measurement of urine and serum nickel suggests a decrease in the absorption of nickel and an increase in the excretion of nickel with longer exposure (Santucci et al. 1994). The observations that orthodontic treatment before ear piercing reduced the prevalence of nickel sensitivity in humans and that nickel sensitivity in mice could be induced by parenteral injection only when oral nickel exposure was reduced (van Hoogstraten et al. 1994) suggest that low levels of oral nickel can prevent induction of nickel sensitivity. Therefore, although some nickel-sensitive persons may react to a single oral dose of nickel, lowering oral intake of nickel to protect all presently sensitive

individuals may serve to increase the population that could be sensitized by dermal exposure to nickel.

Nickel sensitivity has also been induced in guinea pigs by skin painting or intradermal injection (Wahlberg 1976; Zissu et al. 1987) and in mice by dermal contact (Siller and Seymour 1994). Dermal effects in animals after dermal exposure to nickel included distortion of the epidermis and dermis, hyperkeratinization, atrophy of the dermis, and biochemical changes (Mathur et al. 1977, 1988).

Based on human data, environmental exposure or exposure to nickel at hazardous waste sites could result in dermatitis in nickel-sensitized individuals.

Ocular Effects. In an oral study in humans, one subject developed left homonymous hemianopsia (loss of sight in the corresponding lateral half of the eyes) after oral exposure to nickel sulfate in drinking water (Sunder-man et al. 1989b). This effect is discussed further under neurological effects. Ophthalmological examinations did not reveal any changes in the eyes of rats treated by gavage with nickel as nickel chloride for 91 days (American Biogenics Corporation 1988). Based on limited data, ocular effects are unlikely to occur in humans following environmental exposure or exposure to nickel at hazardous waste sites.

Body Weight Effects. Decreased body weight gain was observed in animals after inhalation exposure and oral exposure to high doses of nickel (Ambrose et al. 1976; Dunnick et al. 1989; Seidenberg et al. 1986; Takenaka et al. 1985; Weischer et al. 1980; Whanger 1973). Reduced food and water intake was also observed in animals orally exposed to nickel (RTI 1986, 1988a). Decreased body weight has also been observed in rats given a single intramuscular injection of nickel chloride (Smialowicz et al. 1987). It is not likely that environmental exposure or exposure to nickel at hazardous waste sites will result in body weight effects in humans.

Metabolic Effects. The hyperglycemic effect of nickel is discussed under endocrine effects because it appears to be secondary to the effects on catecholamine release from the adrenal gland and central nervous system and to the effects on insulin release by the pancreas.

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Immunological and Lymphoreticular Effects. Exposure to nickel can lead to sensitization. A significant increase in several immunoglobulins and other serum proteins was observed in workers exposed to nickel (Bencko et al. 1983, 1986). A relationship was found between human lymphocyte antigens (HLA-DRw6) and nickel sensitivity in individuals with a contact allergy (Mozzanica et al. 1990). The relative risk for individuals with DRw6 to develop a sensitivity to nickel was approximately 1: 11.

Researchers using animals did not examine the effect of exposure on serum immunoglobulins or antigens, but immunological effects were found following both inhalation and oral exposure to nickel. A decrease in alveolar macrophage activity was observed after intermediate-duration inhalation exposure to either soluble or less-soluble nickel compounds (Haley et al. 1990). The toxicity ranking was nickel sulfate > nickel subsulfide > nickel oxide. Chronic inhalation exposure of rats and mice to nickel compounds has resulted in hyperplasia of the lung-associated lymph nodes (NTP 1996a, 1996b, 1996c). A decrease in the proliferative response of the bone marrow and spleen was observed following oral exposure of mice (Dieter et al. 1988). Animal data also indicate that nickel exposure may result in a greater s,usceptibility to infection (Johansson et al. 1981; Spiegelberg et al. 1984). A decrease in natural killer (NK) cell activity was observed in rats and mice after parenteral administration of nickel (Smialowicz et al. 1985, 1986, 1987).

As discussed under dermal effects, human data indicate that at least some sensitive individuals will react following environmental exposure or exposure to nickel at hazardous waste sites.

Neurological Effects. An acute exposure to nickel in water from a contaminated drinking fountain caused giddiness, weariness, and headache (Sunderman et al. 1988). Loss of vision was found in one man following ingestion of nickel sulfate (Sunder-man et al. 1989b). Lethargy, ataxia, prostration, irregular breathing, and cool body temperature were observed in rats treated by gavage with nickel chloride (American Biogenics Corporation 1988). Reduction in body temperature has also been observed in animals parenterally exposed to nickel (Gordon 1989; Gordon et al. 1989; Hopfer and Sunderman 1988; Watanabe et al. 1990). Because effects on thermoregulation were observed, the decreased body temperature observed in these studies is probably a neurological effect.

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The limited human data suggest that neurological effects can occur following exposure to nickel at high doses, but these effects are unlikely to result from environmental exposure or exposure to nickel at hazardous waste sites.

Reproductive Effects. An increase in abortion rate has been reported among women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). The contribution of heavy lifting and possible heat stress to this effect is not known. In animals, reproductive effects were observed after inhalation, oral, and parenteral exposure. Testicular effects have been reported following inhalation exposure to nickel compounds at concentrations at which emaciation of the animals was also observed, leading the investigators to question whether the effect was a direct result of nickel exposure (Benson et al. 1987, 1988). A significant increase in the incidence of abnormalities of the head of spermatozoa was also observed in mice after oral exposure to very high doses of nickel (Sobti and Gill 1989). One dermal study reported testicular effects, but it was unclear whether the animals had also been orally exposed by licking the nickel from their skin (Mathur et al. 1977). Subcutaneous and intratesticular injection of rats with nickel compounds has resulted in testicular damage (Hoey 1966; Kamboj and Kar 1964). Following oral exposure, no significant effects on fertility and viability or lactation indices were observed in rats, although a significant increase in gestational duration was observed in a two generation study (RTI 1988a). However, this study was compromised by decreased food and water intake and elevated temperatures. No effect on gestational length was observed, however, in a three-generation study (Ambrose et al. 1976). Results from multigeneration and multilitter studies (RTI 1988a, 1988b; Smith et al. 1993) show a decrease in the number of pups surviving until weaning. Because cross-fostering experiments have not been completed, it is not possible to determine if this effect is a result of a defect in the pups or an effect on the dam that reduces the ability to nurture the pups (Smith et al. 1993). A significant decrease in the number of pregnancies and a decrease in the mean number of implanted embryos per female were observed in mice injected intraperitoneally with nickel chloride or nickel nitrate (Deknudt and Leonard 1982). Subcutaneous injection of rats with nickel, as nickel chloride, during lactation resulted in changes in milk composition (increased milk solids and lipids, decreased protein and lactose) (Dostal et al. 1989), suggesting that deaths of offspring during lactation in oral exposure studies (RTI 1988a, 1988b; Smith et al. 1993) may result from poor nutrition rather than a defect in the offspring.

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Existing data indicate that nickel is a reproductive toxicant in animals, although a clear dose response relationship has not been identified. Occupational exposure to high concentrations of nickel may result in reproductive effects in humans, but it is unlikely that exposure to nickel at low levels expected at hazardous waste sites would result in reproductive effects.

Developmental Effects. Compared to controls, an 11.1% increase in structural malformations (specific types of malformations not stated) was observed in infants of women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). The contribution of heavy lifting and possible heat stress to this effect is not known. Decreased fetal weight was observed in rats exposed to nickel by inhalation (Weischer et al. 1980). Researchers conducting multigeneration and multilitter oral studies in rodents reported developmental effects including increased pup mortality and decreased pup weight (Ambrose et al. 1976; RTI 1988a, 1988b; Smith et al. 1993). In one study, the F_{2b} generation was delivered by laparotomy on day 20 of gestation, and no adverse effects were observed (RTI 1988b). These data indicate that the fetal effects were expressed during the perinatal or postnatal periods and not during gestation. Although the results of the two-part RTI (1988a, 1988b) study may have been compromised by decreased food and water intake and elevated temperatures during some periods, the observation of increased pup mortality was confirmed by Smith et al. (1993). The researchers also reported increased mortality of rat pups from dams treated throughout gestation and lactation. Similar developmental effects were observed in rodents after parenteral administration of nickel (Chernoff and Kavlock 1982; Sunderman et al. 1978). An increase in fetal abnormalities (vertebrae and rib fusions, cleft palate) was observed in mice given a single intraperitoneal dose of nickel chloride on gestation days 7-11 (Lu et al. 1979). The peak incidence of malformations was observed when mice were treated on gestation days 8 or 9 (6.9% in treated animals compared to 0% in controls). Changes in activity were not observed in offspring of mice given a single intraperitoneal injection of nickel chloride on gestation day 8 (Gray et al. 1986). These results indicate that high doses of nickel can result in developmental effects in animals, but it is not known whether occupational exposure to nickel could result in developmental effects in humans. It is unlikely that environmental exposure to nickel would result in developmental effects.

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Genotoxic Effects. The genotoxicity of nickel and compounds *in vivo* and *in vitro* is presented in Tables 2-7 and 2-8, respectively.

A significant increase, compared with controls, in the incidence of chromosomal aberrations (gaps), but not chromosomal breaks or sister chromatid exchanges, was observed in two groups of nickel refinery workers (Waksvik and Boysen 1982). A slight but significant increase in the incidence of chromosomal aberrations was observed in workers exposed to manganese, nickel, and iron (Elias et al. 1989). No correlation was found between nickel exposure levels and the incidence of aberrations. Nickel could not be identified as the sole causal agent because the workers were also exposed to other substances. The limited data indicate that nickel exposure produced genotoxic effects in humans following inhalation exposure.

The equivocal results of mutagenicity tests in bacteria probably reflect the variation in sensitivity of bacterial strains and different conditions of the studies. Results of chromosome aberration tests in cultured mammalian cells generally indicate a positive response. Most of the studies of chromosome aberrations *in vivo* indicate that nickel compounds are not clastogenic; however, one oral study (Sobti and Gill 1989) and one intraperitoneal study (Dhir et al. 1991) reported an increase in the incidence of micronuclei in the bone marrow of mice exposed to various nickel compounds. In the second study, a dose-related increase in chromosome aberrations was observed in the bone marrow cells of mice given a single intraperitoneal injection of nickel chloride (Dhir et al. 1991). Nickel has also been found to be toxic to male germ cells after oral treatment (Sobti and Gill 1989). The results of sister chromatid exchange studies in mammalian cells and cultured human lymphocytes are positive (Andersen 1983; Arrouijal et al. 1992; Larremendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981; Wulf 1980). Data concerning human foreskin cells, mouse embryo fibroblasts, and hamster cells indicate that nickel induces cellular transformation (Biedermann and Landolph 1987; Conway and Costa 1989; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stem 1984; Miura et al. 1989; Saxholm et al. 1981). The induction of cellular transformation by a particular nickel compound is proportional to its cellular uptake (Costa 1989; Costa and Heck 1982; Costa and Mollenhauer 1980). Crystalline nickel subsulfide, a carcinogen that induces cellular transformation, was actively phagocytized by Syrian hamster embryo cells (Costa and Heck 1982; Costa and Mollenhauer 1980). Phagocytosis and cellular transformation were negligible, however, for amorphous nickel monosulfide.

Table 2-7. Genotoxicity of Nickel *In Vivo*

Species (test system)	End point	Result	Reference	Compound
Drosophila melanogaster	Gene mutation	–	Rasmuson 1985	Nickel nitrate or chloride
D. melanogaster	Recessive lethal	+	Rodriquez-Arnaiz and Ramos 1986	Nickel sulfate
D. melanogaster	Gene mutation (wing spot test)	±	Ogawa et al. 1994	Nickel chloride
Mammalian cells:				
Human lymphocytes	Chromosome aberrations (gaps)	+	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
Human lymphocytes	Sister chromatid exchange	–	Waksvik and Boysen 1982	Nickel oxide, nickel subsulfide
Rat bone marrow and spermatogonial cells	Chromosome aberrations	–	Mathur et al. 1978	Nickel sulfate
Mouse bone marrow cells	Micronucleus test (oral)	+	Sobti and Gill 1989	Nickel chloride, nickel sulfate, nickel nitrate
Mouse bone marrow cells	Chromosome aberrations (ip)	+	Dhir et al. 1991	Nickel chloride
Mouse bone marrow cells	Micronucleus test (ip)	–	Deknudt and Leonard 1982	Nickel chloride
Mouse	Dominant lethal (ip)	–	Deknudt and Leonard 1982	Nickel acetate

– = negative result; + = positive result; ± = weakly positive; (ip) = intraperitoneal

Table 2-8. Genotoxicity of Nickel *In Vitro*

Species (test system)	End point	Result	Reference	Compound
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	Arlauskas et al. 1985; Biggart and Costa 1986; Marzin and Phi 1985; Wong 1988	Nickel chloride, nickel nitrate, nickel sulfate
Escherichia coli	Gene mutation	–	Green et al. 1976	Nickel chloride
Escherichia coli	DNA replication	+	Chin et al. 1994	Nickel chloride
Cornebacterium sp.	Gene mutation	+	Pikalek and Necasek 1983	Nickel chloride
Bacillus subtilis	DNA damage	–	Kanematsu et al. 1980	Nickel oxide and trioxide
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae	Gene mutation	–	Singh 1984	Nickel sulfate
Mammalian cells:				
CHO cells	Gene mutation	+	Hsie et al. 1979	Nickel chloride
Virus-infected mouse cells	Gene mutation	+	Biggart and Murphy 1988; Biggart et al. 1987	Nickel chloride
Mouse lymphoma cells	Gene mutation	+	Amacher and Paillet 1980; McGregor et al. 1988	Nickel chloride, nickel sulfate
Chinese hamster V79 cells	Gene mutation	+	Hartwig and Beyersmann 1989; Miyaki et al. 1979	Nickel chloride
CHO cells	DNA damage	+	Hamilton-Koch et al. 1986; Patierno and Costa 1985	Crystalline NiS, nickel chloride
Human diploid fibroblasts	DNA damage	–	Hamilton-Koch et al. 1986	Nickel chloride
Human gastric mucosal cells	DNA damage	–[b]	Pool-Zobel et al. 1994	Nickel sulfate

Table 2-8 (*continued*)

Species (test system)	End point	Result	Reference	Compound
CHO AS52 cells	Gene mutation	+	Fletcher et al. 1994	Nickel oxide (black and green); amorphous nickel sulfide; nickel subsulfide nickel chloride; nickel sulfate; nickel acetate
Human HeLa cells	DNA replication	+	Chin et al. 1994	Nickel chloride
Hamster cells	Sister chromatid exchange	+	Andersen 1983; Larremendy et al. 1981; Ohno et al. 1982; Saxholm et al. 1981	Nickel sulfate, nickel chloride; crystalline NiS
Human lymphocytes	Sister chromatid exchange	+	Andersen 1983; Larremendy et al. 1981; Saxholm et al. 1981; Wulf 1980	Nickel sulfate, nickel sulfide
Hamster cells	Chromosome aberration	+	Conway and Costa 1989; Larremendy et al. 1981; Sen and Costa 1986b; Sen et al. 1987	Nickel sulfate, nickel chloride, nickel monosulfide
Human lymphocytes	Chromosome aberration	+	Larremendy et al. 1981	Nickel sulfate
Human lymphocytes	Sister chromatid exchange	+	Arrouijal et al. 1982	Nickel subsulfide
	Metaphase analysis			
	Micronucleus	+		
		+		
Human bronchial epithelial cells	Chromosome aberration	+	Lechner et al. 1984	Nickel sulfate

Table 2-8 (*continued*)

Species (test system)	End point	Result	Reference	Compound
Hamster cell and C3H/10T1/2 cells	Cell transformation	+	Conway and Costa 1989; Costa and Heck 1982; Costa and Mollenhauer 1980; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stern 1984; Saxholm et al. 1981	Nickel monosulfide, nickel subsulfide, nickel chloride, nickel, nickel oxide or trioxide
Mouse embryo fibroblasts	Cell transformation	–	Miura et al. 1989	Nickel sulfate, nickel chloride
Mouse embryo fibroblasts	Cell transformation	+	Miura et al. 1989	Nickel subsulfide, nickel monosulfide, nickel oxide
Human foreskin cells	Cell transformation	+	Biedermann and Landolph 1987	Nickel subsulfide, nickel oxide, nickel sulfate, nickel acetate

[a]Metabolic activation is not an issue for nickel compounds.
[b]Nickel was genotoxic and cytotoxic at the same concentration (9.5 µmol/mL), so it was not a selective genotoxicant.

– = negative result; + = positive result; ++ = highly positive; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NiS = nickel sulfide

2. HEALTH EFFECTS

The genotoxicity of nickel subsulfide was examined in human lymphocytes from nickel-sensitized individuals and from individuals not sensitized to nickel (Arrouijal et al. 1992). Compared to lymphocytes from sensitized individuals, lymphocytes from those not sensitized to nickel took up more nickel and showed a greater increase in clastogenic activity, as determined by the metaphase analysis and micronucleus tests. This study and the other *in vitro* and *in vivo* genotoxicity data indicate that if nickel can get inside the cells it is genotoxic. Nickel has been reported to interact with DNA, resulting in crosslinks and strand breaks (Ciccarelli and Weterhahn 1982; Patiemo and Costa 1985, 1987; Robinson and Costa 1982).

A high level of mutagenicity (30-40 times background) has been found for less-soluble nickel compounds (nickel sulfide, nickel subsulfide, green and black nickel oxides) at the guanine phosphoribosyl transferase gene in the Chinese hamster G12 cell line (Klein et al. 1994). In contrast to these findings, the nickel compounds were not very mutagenic (from two to three times background) in the Chinese hamster G12 cell line where the guanine phosphoribosyl gene was integrated at a different location. The soluble nickel sulfate was not very mutagenic (four times background) in either cell line. The investigators suggest that nickel mutagenesis in the G12 cells may be related to the integration of the guanine phosphoribosyl sequence into a heterochromatic region of the genome.

Cancer. The carcinogenic effect of nickel has been well documented in occupationally exposed workers. Nickel refinery dust, believed to have been mostly nickel subsulfide, has been classified as a class A human carcinogen by EPA (IRIS 1996). IARC (1990) has concluded that there is sufficient evidence from human exposure to establish the carcinogenicity of nickel sulfate and the combinations of nickel sulfides and oxides. For metallic nickel, there are inadequate human data but sufficient evidence of carcinogenicity in animals. From animal studies, there are sufficient data for nickel monoxides, nickel hydroxides, and crystalline nickel sulfides; limited evidence for nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides, and nickel telluride; and inadequate evidence for nickel trioxide, amorphous nickel sulfide, and nickel titanate. IARC (1990) has classified nickel and nickel compounds as group 1, human carcinogens, and metallic nickel as group 2B, possible human carcinogen. Based on occupational data, EPA has calculated slope factors and risk factors for nickel refinery dust (see Figure 2-l for the estimated upper-bound human cancer risk level). The slope factors were based on the incidence of lung cancer in cohorts of nickel refinery workers (Chovil et al. 1981; Doll et

al. 1977; Enterline and Marsh 1982; Magnus et al. 1982). The risk of developing respiratory tract cancers was markedly decreased when the date of first exposure was later than ≈1930 (Doll et al. 1970, 1977; Pedersen et al. 1973). This was the result of reducing nickel exposure by increasing protective measures' at the nickel refineries. The respiratory cancers were primarily related to exposure to less-soluble compounds at ≥10 mg nickel/m^3 (International Committee on Nickel Carcinogenesis in Man 1990), which is much higher than ambient air levels of nickel. The interaction between smoking and nickel exposure on lung cancer has been found to be additive rather than multiplicative (Magnus et al. 1982).

Lung tumors were observed in rats after inhalation exposure to nickel subsulfide (Ottolenghi et al. 1974). Two-year inhalation carcinogenicity bioassays have shown nickel oxide and nickel subsulfide to be carcinogenic in rats resulting in alveolar/bronchiolar adenomas and carcinomas and benign and malignant pheochromocytomas of the adrenal medulla (Dunnick et al. 1995; NTP 1996a, 1996b). In mice, there was no evidence of a carcinogenic effect of nickel subsulfide in either sex, no evidence of a carcinogenic effect of nickel oxide in males, and equivocal evidence of carcinogenic activity of nickel oxide in females based on alveolar/bronchiolar adenomas and carcinomas. Although nickel sulfate was the most toxic nickel compound, it was not carcinogenic in either rats or mice (NTP 1996c).

Following parenteral exposure, tumors of the lung and at the site of injection were observed. The less-soluble nickel compounds (nickel subsulfide, nickel oxide) were generally more carcinogenic than the soluble nickel compounds (nickel metal, nickel monosulfide) following parenteral administration (Gilman 1962; Kasprzak et al. 1983; Lumb and Sunderman 1988; Smialowicz et al. 1985; Sunderman and Maenza 1976; Sunderman and McCully 1983). Nickel oxide compounds calcinated at lower temperatures were found to be much more active in terms of producing preneoplastic and neoplastic changes in rats (intrarenal injection) than those calcinated at higher temperatures (Sunder-man et al. 1987).

Although the evidence is sufficient to consider less-soluble nickel compounds carcinogens following inhalation exposure, how environmental exposure to nickel affects cancer risk is not clear. Nickel levels in the environment are much lower than those that were associated with cancer in workers. In the environment, the nickel is also more likely to be in the form of a mineral lattice rather than the more active nickel refinery dust which contains nickel subsulfide, the form of nickel most

consistently associated with cancer. Although soluble nickel compounds may not be directly carcinogenic, as indicated by the negative results in the nickel sulfate bioassay (NTP 1996c), inhalation of nickel sulfate did result in an inflammatory response in the lungs of animals. Because sustained tissue damage can serve to promote carcinogenesis, epidemiology studies of humans who are exposed to many substances may not be able to distinguish between the carcinogenic activity of less-soluble nickel compounds and the promoting activity of toxic concentrations of soluble nickel compounds.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to nickel are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or

cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial ceils), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by nickel are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Nickel

Biological monitoring data are available primarily from occupational settings. Determination of nickel in the urine, feces, serum, hair, and nasal mucosa has been used to demonstrate human exposure to nickel compounds (Angerer and Lehnert 1990; Bencko et al. 1986; Bemacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Torjussen and Andersen 1979). Serum and urine levels of nickel have been the most often studied.

Significant correlations have been found between occupational exposure to less-soluble nickel compounds (breathing zone samples) and the levels of nickel in the urine and serum in various groups of workers (Morgan and Rouge 1984). Nickel levels in urine and serum of workers inhaling nickel powder, alloys, or slightly soluble compounds reflect the combined influences of long-term accumulation and recent exposures (Sunderman et al. 1986). Correlations between exposure concentration and levels in the urine and serum were found only in groups and not in individual workers. A relationship between exposure concentrations of soluble nickel compounds and levels of nickel in the urine and serum has also been reported (Bemacki et al. 1980). Urine and serum levels of nickel in workers inhaling soluble nickel compounds reflect the amount of nickel absorbed in the previous 1 or 2 days (Sunderman et al. 1986). With respect to monitoring nickel following exposure to soluble compounds, the best correlations between exposure concentration and urine levels were found with "end-of-shift" urine sampling (Bemacki et al. 1980)

or “next morning” urine sampling (Tola et al. 1979). A correlation was found between urinary nickel and plasma nickel in workers, with nickel levels in urine being about eightfold higher than plasma levels (Angerer and Lehnert 1990; Bernacki et al. 1978).

Higher concentrations of nickel in the urine and the plasma and lower concentrations of nickel in the nasal mucosa were observed in workers exposed to soluble nickel compounds when compared to workers exposed to less-soluble compounds (Bemacki et al. 1978; Torjussen and Andersen 1979). Less-soluble nickel compounds tended to remain in the nasal mucosa (half-life of ≈3.5 years); therefore, urinary and plasma levels were relatively low (Torjussen and Andersen 1979).

In workers exposed to nickel at a battery factory, a positive correlation was also found between air concentrations of nickel and concentrations of nickel in the feces (Hassler et al. 1983). High concentrations of nickel were found in the feces of workers exposed to nickel dusts containing large particles (as a result of greater mucociliary clearance from the lungs to the gastrointestinal tract) (Hassler et al. 1983).

In nickel electroplating workers, urinary concentrations of nickel were not found to be correlated with air concentrations of soluble nickel compounds which ranged from 0.1 to 42 $\mu g/m^3$ (Bavazzano et al. 1994). Measurement of nickel on the face and hands of these workers indicated that skin contamination, especially facial skin, plays an important role in the nickel exposure of these workers.

Exposure to nickel has also been monitored by assessing the content of nickel in the hair (Bencko et al. 1986). Analysis of the nickel content of hair provides evidence of past exposure and not changes in recent exposure to nickel. Correlations between exposure concentration and the level of nickel in hair were not reported.

Sunderman (1993) reviewed all the biological monitoring data for nickel in humans and concluded that the most useful specimens for biological monitoring are urine and serum. Levels of nickel in urine and serum can provide the most information about levels of nickel exposure if the route, sources, and duration of exposure are known, if the chemical identities and physical-chemical properties of the nickel compounds are known, and if physiological information, for example renal function, of the exposed population is known (Sunderman 1993).

Sensitization to nickel causes changes in serum antibodies (an increase in IgG, IgA, and IgM and a decrease in IgE) that may be monitored to determine if exposure to nickel has occurred (Bencko et al. 1983, 1986; Novey et al. 1983). These changes were found in both sensitized (Novey et al. 1983) and nonsensitized (Bencko et al. 1983, 1986) individuals. Information regarding the exposure concentration of nickel needed to cause serum antibody changes was not reported.

2.6.2 Biomarkers Used to Characterize Effects Caused by Nickel

Are levels of nickel in urine or serum indicators of specific health effects in humans? After reviewing monitoring data in occupationally exposed workers, Sunderman (1993) concluded that with the exception of nickel carbonyl, "nickel concentrations in body fluids should not be viewed as indicators of specific health effects." Sunderman (1993) did suggest that for persons exposed to soluble nickel compounds (e.g., nickel chloride, nickel sulfate) an increase in nickel concentrations in body fluids is a signal to reduce exposure, and the absence of increased values indicates nonsignificant exposure. For persons exposed to less-soluble nickel compounds (e.g., nickel subsulfide, nickel oxide), increases in nickel concentrations in body fluids indicate significant absorption, and exposure should be reduced to the lowest level attainable. In contrast to soluble nickel compounds, the absence of increased nickel in body fluids does not mean freedom from health risks (e.g., lung and nasal cancers) that have been observed following occupational exposure to less-soluble nickel compounds. Because the form of nickel is rarely known in environmental exposures, increased nickel in the serum and urine of the general population cannot be used to predict health effects. Nickel concentrations in the serum and urine of persons not occupationally exposed are <0.05-1.3 μg/L and <0.1-13.3 μg/L, respectively (Sunderman 1993).

Antibodies to hydroxymethyl uracil, an oxdized DNA base, were determined in workers exposed to nickel and cadmium, and in welders (Frenkel et al. 1994). Compared to controls, a significant increase in these antibodies was noted in the most highly exposed workers. Personal monitoring of 12 workers exposed to nickel and cadmium showed correlation coefficients between exposure concentrations and the antibodies of 0.4699 for cadmium and 0.7225 for nickel. Antibodies to hydroxymethyl uracil were not increased among welders. The levels of antibodies in the control populations for the nickel cadmium workers and for the welders were different indicating the importance of determining the distribution of a new biomarker in controls for each population that

is studied. This preliminary study suggests that antibodies to oxidized DNA products may be useful biomarkers for nickel and other metals that induce oxidative stress.

A preliminary study using imaging cytometry of nasal smears obtained from nickel workers indicates that this method may be useful to detect precancerous and cancerous lesions (Reith et al. 1994). With this method in which the cells were obtained by brushing the inside of the nose, the investigators were able to distinguish between nickel-exposed workers with non-dysplastic normal and suspicious mucpsa smears and those with dysplastic lesions.

Although increases in oxidized DNA products and precancerous and cancerous lesions in the nose have been associated with nickel exposure, these effects are not specific to nickel. There are no specific biomarkers for nickel health effects.

2.7 INTERACTIONS WITH OTHER CHEMICALS

A number of interactions of nickel with other chemicals are reported in the literature. The toxicity of nickel has been mitigated by treatment with chelating agents (Horak et al. 1976; Misra et al. 1988; Sunder-man et al. 1976). Chelation treatment stimulates the excretion of nickel, thereby mitigating its toxicity. Lipophilic chelating agents, such as triethylenetetramine (TETA) and Cyclam (1,4,8,1l-tetraazacyclotetradecane), were more effective than hydrophilic chelating agents such as EDTA, cyclohexanediamine tetraacetic acid (CDTA), diethylenetriamine pentaacetic acid (DTPA), and hydroxyethylenediamine triacetic acid (HEDTA) (Misra et al. 1988). The higher efficacy of the lipophilic agents may be due to their ability to bind to nickel both intracellularly and extracellularly, while the hydrophilic agents can only bind extracellularly.

A cross-reactivity between nickel and cobalt in sensitive individuals has been noted. For example, eight patients with asthma resulting from cobalt exposure also developed asthma when challenged with nickel sulfate (Shirakawa et al. 1990).

Nickel has also been found to interact with other metals such as iron, chromium, magnesium, manganese, zinc, and cadmium. The toxicity of nickel was mitigated by treatment with zinc (Waalkes et al. 1985) and magnesium (Kasprzak et al. 1986). The data suggest that magnesium, but not zinc, acted by altering the pharmacokinetics of nickel. The mechanism of action for zinc

could not be determined from the study (Waalkes et al. 1985). Coadministration of magnesium and nickel resulted in increased urinary excretion of nickel and decreased deposition of nickel in the lung, liver, and kidney (Kasprzak et al. 1986). Manganese dust inhibited nickel subsulfide-induced carcinogenesis following simultaneous intramuscular injection of the two compounds (Sunderman and McCully 1983). The inhibition by manganese was a local and not a systemic effect.

Pretreatment of animals with cadmium 1 week before nickel treatment enhanced the nephrotoxicity and hepatotoxicity of nickel (Khandelwal and Tandon 1984). The mechanism of interaction could not be determined from these studies. Pretreatment of mice with cadmium 24 hours before nickel treatment has also been shown to decrease nickel-induced lethality and lipid peroxidation in the liver (Srivastava et al. 1995). The investigators suggested that a cadmium-induced production of ceruloplasmin, which prevented a nickel-induced reduction of ceruloplasmin, provided the protection against nickel toxicity.

More severe respiratory effects (increased lung weight, increase in the accumulation of alveolar macrophages, increase in the density of type II cell volumes) were observed in rabbits exposed by inhalation to both nickel and trivalent chromium than in rabbits exposed to nickel only (Johansson et al. 1988b).

In iron-deficient rats, nickel enhanced the absorption of iron (Nielsen 1980; Nielsen et al. 1980, 1984). This effect of nickel was only observed when ferric sulfate was given. No interaction was observed when iron was given as a 60% ferric/40% ferrous sulfate mixture. It has been proposed that nickel facilitates the passive diffusion of ferric ions by stabilizing the transport ligand (Nielsen 1980).

Veien and Menne (1990) have suggested that vasoactive substances found in food can enhance nickel sensitivity reactions. Foods that they suggested that nickel-sensitive people should avoid include beer, wine (especially red wine), herring, mackerel, tuna, tomatoes, onions, carrots, apples, and citrus fruits. The vasoactive substances may increase the amount of nickel that is able to reach the skin.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to nickel than will most persons exposed to the same level of nickel in the environment. Reasons may include genetic makeup, age, health, and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of nickel, or compromised function of organs affected by nickel. Populations who are at greater risk due to their unusually high exposure to nickel are discussed in Section 5.6, Populations With Potentially High Exposures.

Individuals sensitized to nickel may be unusually susceptible because exposure to nickel by any route may trigger an allergic response. Epidemiology studies indicate that blacks have a higher nickel sensitivity than whites and that women of both racial groups have higher reaction rates than men (Nethercott and Holness 1990; North American Contact Dermatitis Group 1973; Prystowsky et al. 1979). The incidence of reactions may be higher in women because they generally wear more metal jewelry than men. Further studies are required to determine if there are true gender and racial differences in nickel sensitivity, or if it is indeed a difference in exposure.

A relationship between HLA and nickel sensitivity was observed in patients who had a contact allergy and positive results in a patch test for nickel (Mozzanica et al. 1990). The nickel-sensitive group had a significant elevation in HLA-DRw6 antigen, compared to normal controls. The relative risk for patients with DRw6 to develop a sensitivity to nickel was approximately 1:ll. The presence of DRw6 may be monitored to determine the potential risk of individuals to become sensitized to nickel.

Nickel that has been absorbed into the blood stream is primarily excreted in the urine. Therefore, individuals with kidney dysfunction are likely to be more sensitive to nickel. The increased sensitivity of persons with kidney disfunction is also suggested by increased serum concentrations of nickel in dialysis patients (Hopfer et al. 1989). Because diabetics often have kidney damage, and because of the hyperglycemic effects of nickel observed in animal studies, the sensitivity of diabetics to nickel is also likely to be increased.

2. HEALTH EFFECTS

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to nickel. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to nickel. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to nickel: Bronstein and Currance 1988; Gosselin et al. 1984; Stutz and Janusz 1988.

2.9.1 Reducing Peak Absorption Following Exposure

General recommendations for reducing absorption of nickel following acute inhalation exposure have included moving the patient to fresh air and monitoring for respiratory distress (HSDB 1996). About 20-35% of less-soluble nickel deposited in the lungs is absorbed into the blood from the respiratory tract (see Section 2.3.1.1). The nickel that is not absorbed into the blood is removed by mucociliary action and is expectorated or swallowed. Since the oral toxicity of metallic nickel is low, treatment with fluid and electrolyte replacement has been considered necessary only in cases with severe vomiting and diarrhea (HSDB 1996), which can occur as a result of nickel-induced gastrointestinal irritation (Sunderman et al. 1988). Thus, further induction of emesis is seldom necessary. EDTA added to the diet of humans decreased the bioavailability of orally administered nickel (Solomons et al. 1982). The presence of food in the stomach also reduced the gastrointestinal absorption of nickel (Christensen and Lagesson 1981). Oral administration of water or milk helps to dilute caustic nickel compounds in the stomach (Bronstein and Currance 1988; Stutz and Janusz 1988). In cases of dermal or ocular exposure, the skin or eyes should be thoroughly washed to prevent absorption by the skin or irritation of the eyes (Bronstein and Currance 1988; Stutz and Janusz 1988). Topical application of chelating agents and barrier creams have also been used to reduce dermal absorption in nickel-sensitive subjects (Gawkrodger et al.1995). The most effective topical ligand for nickel yet described is 5-chloro-7-iodoquinolin-8-o1, but its use may be limited by its toxicity. Propylene glycol, petrolatum, and lanolin have been shown to reduce the dermal absorption of nickel.

2.9.2 Reducing Body Burden

Once absorbed into the blood, nickel has been found to distribute to the kidneys, liver, heart, fat, peripheral nervous tissues, and brain of animals (see Section 2.3.2). A mean serum half-time of nickel of 60 hours was measured in humans after oral exposure to nickel sulfate and nickel chloride (Sunderman et al. 1988).

A number of methods to decrease the body burden of nickel have been used or suggested. As discussed in Section 2.7, chelation treatment with a number of agents has been helpful (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). Lipophilic chelating agents such as TETA and Cyclam were more effective than hydrophilic chelating agents such as EDTA, CDTA, DTPA, and HEDTA (Misra et al. 1988). This may reflect differences in the distribution of hydrophilic and lipophilic agents between the intracellular and extracellular compartments. The use of diethyldithiocarbamate (DDC) as a chelating agent has been suggested as the preferred agent (Goldfrank et al. 1990; HSDB 1996). Disulfiram, which is metabolized to two molecules of DDC, might also be effective if DDC is not available. Penicillamine has also been used as a chelating agent for nickel. Intravenous infusion of fluids reduced the half-time for serum clearance of nickel from 60 to 27 hours in humans who were exposed to nickel sulfate and nickel chloride in water from a contaminated water fountain (Sunderman et al. 1988). The use of chelating agents over the long term to reduce nickel body burden in nickel-sensitive individuals is not recommended because it would also result-in the reduction of other essential metals (Veien and Menne 1990). A nickel restricted diet is useful in some sensitive adults for reducing nickel dermatitis, but this diet must be used with caution in nickel-sensitive children because it may not provide sufficient levels of nutrients for growth (Veien and Menne 1990).

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Many toxic effects of both soluble nickel and some relatively less-soluble (in water) nickel compounds, which slowly dissolve in serum and cytosol, are due to nickel ions (Sunder-man and Oskarsson 1991). In addition to reducing body burden of nickel, chelating agents may effectively mitigate toxicity by binding to nickel ions before toxic effects can be produced. For example, contact dermatitis is a prevalent allergic response to nickel, and disulfiram has been shown to be effective in clearing up cases of nickel dermatitis (Goldfrank et al. 1990; HSDB 1996).

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In human serum, nickel binds to albumin, $_{L}$-histidine, and α-macroglobulin (Sarkar 1984). The principal binding locus of nickel to serum albumin is the histidine residue at the third position from the amino terminus (Hendel and Sunderman 1972). A proposed transport model involves the removal of nickel from albumin to histidine via a ternary complex composed of albumin, nickel, and L-histidine. The low molecular weight $_{L}$-histidine nickel complex can cross biological membranes (Sarkar 1984). How nickel gets inside of cells may determine the effects of the nickel compounds. If nickel ions are taken into the cytosol and bind to protein, they are not delivered to the nucleus, which prevents the interaction of nickel ions with DNA. Crystalline nickel compounds are phagocytized and nickel ions are delivered to the nucleus where they interact with DNA or DNA protein complexes (Costa 1995).

Inhalation exposure to nickel or nickel compounds (along with other metals) in the workplace has resulted in such respiratory effects as chronic bronchitis, emphysema, reduced vital capacity, and asthma (see Section 2.2.1.2). Studies in animals have indicated that the effects of nickel compounds on the respiratory system (chronic inflammation, fibrosis, macrophage hyperplasia) depend on the solubility of the compounds rather than on lung burden. Nickel oxide (low solubility) was less toxic than the soluble nickel sulfate but resulted in a higher lung burden. Nickel compounds have been shown to have effects on lung macrophages of animals, including accumulation of macrophages and granular material in the alveoli and an increase in volume density of alveolar type II cells. The macrophage effects may have been due to the high amounts of surfactant produced by the hyperplastic type II cells, and nickel ions appeared to have a direct effect on type II cells (Johansson and Camner 1986). A decrease in alveolar macrophage activity was observed in animals after exposure to nickel compounds, and the more-soluble compounds had the greatest effect (Haley et al. 1990). The relationship between the effects on alveolar macrophages and respiratory toxicity is unknown, but since soluble nickel compounds appear to have greater effects, the involvement of the nickel ion is implicated.

Nickel subsulfide produced erythrocytosis in animals by increasing renal production of erythropoietin (Hopfer and Sunderman 1978; Hopfer et al. 1984). The mechanism for increased production of erythropoietin is unclear, but coadministration of manganese inhibited the erythrocytosis. Furthermore, nickel has also been found to have a role in the absorption of the ferric ion, resulting in increased hemoglobin levels and hematocrit (Nielsen 1980; Nielsen et al. 1980, 1984). Whether these mechanisms of increased erythropoiesis are related is not clear. Short-

term restriction of dietary intake of iron until chelation therapy is started has been shown to be useful to prevent the increase in hemoglobin and hematocrit in a group of individuals who drank water heavily contaminated with nickel (Sunderman et al. 1988).

In conclusion, it appears that the toxicity of nickel and nickel compounds involves the binding of nickel ions to biological macromolecules. Chelation therapy appears to be effective both in reducing the body burden of nickel and interfering with the mechanism by which nickel exerts toxic effects by competing with the binding sites on biological molecules.

2.10 ADEQUACY OF THE DATABASE

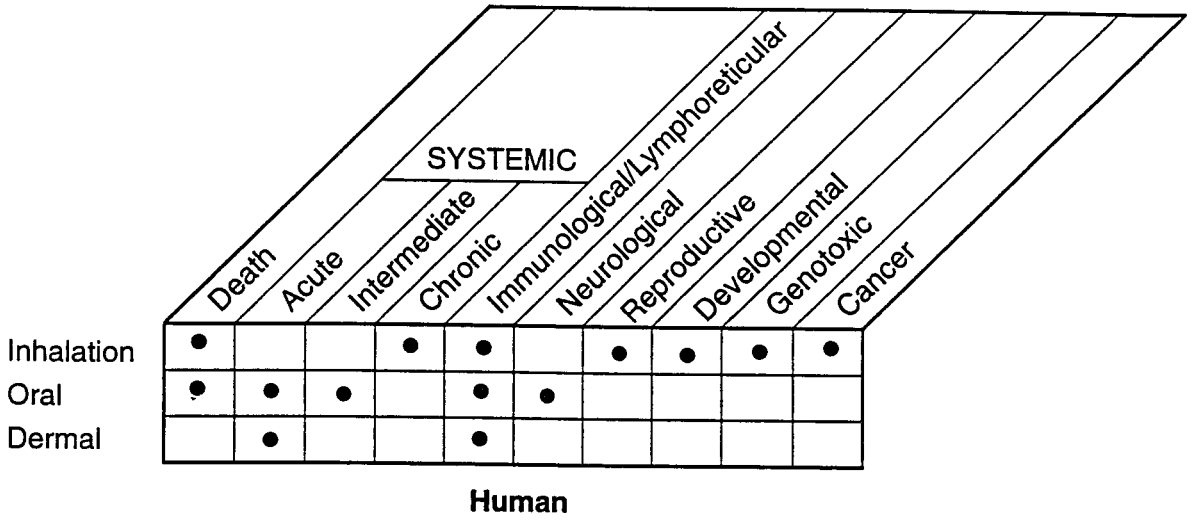
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of nickel is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of nickel.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

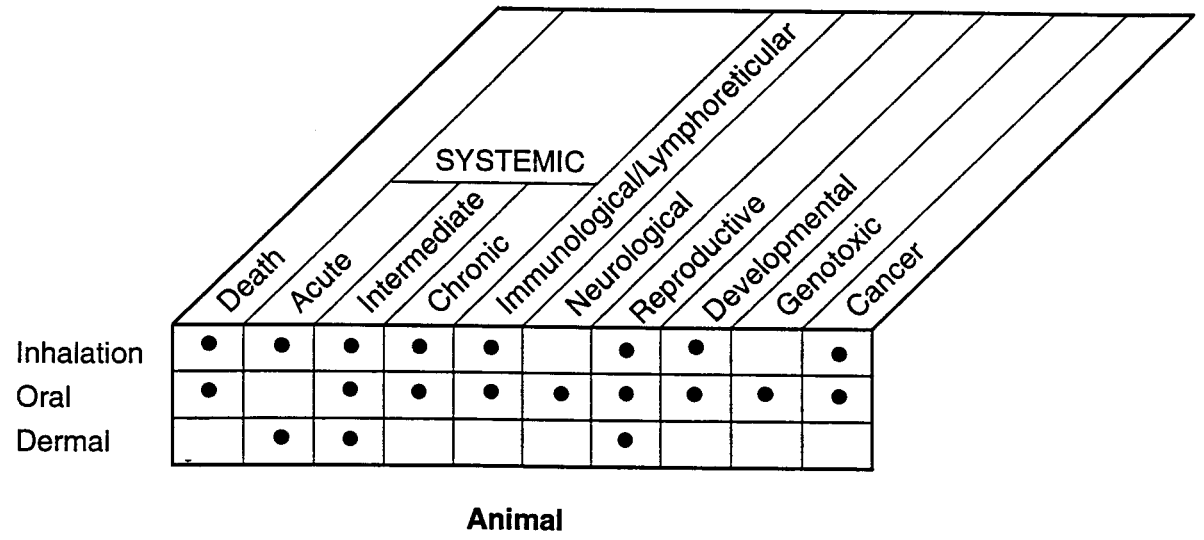
2.10.1 Existing Information on Health Effects of Nickel

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to nickel are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of nickel. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this

FIGURE 2-5. Existing Information on Health Effects of Nickel



Human



Animal

● Existing Studies

figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Humans have been exposed to nickel in nickel mines and processing plants, and numerous epidemiology studies have been performed to assess the cause of death in these workers. Accidental ingestion of nickel also has been documented in a small child and in electroplating workers. Nickel dermatitis is the most prevalent effect of nickel in humans.

Several chronic inhalation and oral studies and acute dermal studies in animals are reported in the literature. These studies exposed several species of animals to both soluble and less-soluble nickel compounds. The target organs were found to be the respiratory system for inhalation exposure and the respiratory system, gastrointestinal tract, hematological system, and kidneys for oral exposure at high levels. Reproductive and developmental effects were observed in animals after inhalation exposure and after oral exposure to nickel. Nickel sensitivity and dermatitis were also observed.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. Acute inhalation exposure to very high concentrations of small particle size metallic nickel has resulted in the death of one subject from adult respiratory distress syndrome (Rendall et al. 1994). A small child died from cardiac arrest after accidental ingestion of nickel sulfate (Daldrup et al. 1983). Numerous health effects (gastrointestinal, hematological, muscular, renal, and neurological) were observed in workers who ingested nickel and boric acid in water from a contaminated drinking fountain (Sunderman et al. 1988). The contribution of boric acid to these effects is not known. Patch testing and oral nickel challenge have been done on individuals with contact dermatitis to determine if an allergy to nickel exists (Christensen and Moller 1975; Cronin et al. 1980; Eun and Marks 1990; Gawkrodger et al. 1986; Jordan and King 1979; Kaaber et al. 1978; Nielsen et al. 1990; Sjovall et al. 1987; Veien et al. 1987). Doseresponse testing in nickel-sensitive individuals suggests that few people will respond at concentrations of ≤100 ppm nickel placed directly on the skin (Menne and Calvin 1993). Alloys

releasing nickel at a rate less than 0.5 μg/cm^2/week are also unlikely to elicit a response in nickel sensitive individuals (Menne et al. 1987).

Acute inhalation studies in animals of nickel sulfate, nickel subsulfide, and nickel oxide revealed nickel sulfate as the most toxic compound (Benson et al. 1987, 1988; NTP 1996a, 1996b, 1996c). A minimal LOAEL following inhalation exposure to nickel sulfate was not identified (Benson et al. 1988). Additional acute inhalation studies of soluble nickel compounds should be completed to identify an acute minimal LOAEL and NOAEL. Because the half-life of less-soluble nickel compounds in the lungs is long, additional acute studies of less-soluble nickel compounds should have long observation periods following exposure.

Acute oral studies in animals are limited to LD_{50} studies (Haro et al. 1968; Mastromatteo 1986). Accidental oral exposure of humans to nickel (Sunder-man et al. 1988) and a longer term study in which dogs vomited during the first few days of the study (Ambrose et al. 1976) indicate that an acute dose of nickel is a gastrointestinal irritant. Therefore, animals that are capable of vomiting may be the most appropriate for further studies of the effects of nickel following acute oral exposure.

The development of nickel sensitivity in mice has been shown to be related to both the concentration of the nickel solution applied to the skin and the duration of exposure (Siller and Seymour 1994). Male mice showed a weaker response than females, and further studies regarding the gender difference in the development of nickel sensitivity would be useful.

Intermediate-Duration Exposure. Intermediate-duration inhalation studies in humans were not located. From the results of numerous animal inhalation studies, NOAELs and/or LOAELs have been identified for respiratory (Benson et al. 1989; Dunnick et al. 1989; Horie et al. 1985; Johansson and Camner 1986; Johansson et al. 1981; NTP 1996a, 1996b, 1996c; Tanaka et al. 1988), hematological (Weischer et al. 1980), hepatic (Benson et al. 1989; Hueper 1958; Weischer et al. 1980), renal (Weischer et al. 1980), immunological (Benson et al. 1989; Dunnick et al. 1988; Haley et al. 1990; Spiegelberg et al. 1984), developmental (Weischer et al. 1980), and reproductive (Benson et al. 1989) effects. The respiratory system had the lowest LOAEL value associated with effects. Intermediate-duration oral exposure of nickel-sensitive women to nickel sulfate at 0.01-0.03 mg/kg/day resulted in improvement of nickel dermatitis (Santucci et al. 1994). Effects

noted in intermediate-duration oral studies in animals at doses of ≥1.3 mglkglday include hematological effects (American Biogenics Corporation 1988; Weischer et al. 1980; Whanger 1973), hepatic effects (Ambrose et al. 1976; American Biogenics Corporation 1988; Dieter et al. 1988; Weischer et al. 1980), and reproductive effects (Ambrose et al. 1976; RTI 1988a, 1988b; Smith et al. 1993).

Dose-response data for dermal exposure of humans or animals to nickel were not identified. The thresholds for nickel sensitivity identified for acute dermal exposure of humans (Menne and Calvin 1993; Menne et al. 1987) should be protective for longer term exposure.

Chronic-Duration Exposure and Cancer. Epidemiology studies regarding occupational exposure to nickel in mines or in nickel processing plants are available (Bencko et al. 1983, 1986; Cornell and Landis 1984; Poled& 1981; Sunderman and Horak 1981). Chronic oral or dermal studies in humans were not located. From the results of animal chronic inhalation studies, LOAELs and NOAELs were identified for respiratory effects (NTP 1996a, 1996b, 1996c; Ottolenghi et al. 1974; Taker&a et al. 1985; Wehner 1986; Wehner et al. 1975, 1979). A chronic-duration inhalation MRL of $2x10^{-4}$ mg nickel/m^3 was based on a NOAEL of 0.3 mg nickel/m^3 for effects in rats exposed to nickel sulfate in a 2-year study (NTP 1996b). This chronic-duration inhalation MRL should also be protective of intermediate-duration exposure. Data are insufficient for the derivation of a chronic oral MRL, and additional chronic oral data are needed.

Findings from epidemiology studies (Chovil et al. 1981; International Committee on Nickel Carcinogenesis in Man 1990; Doll et al. 1977; Enterline and Marsh 1982; Magnus et al. 1982; Pedersen et al. 1973; Sunderman et al. 1989a) identify less-soluble nickel compounds as carcinogenic following inhalation exposure. The epidemiological evidence also suggests that soluble nickel compounds may promote the development of cancer especially when less-soluble nickel compounds are present (International Committee on Nickel Carcinogenesis in Man 1990). Nickel subsulfide (NTP 1996b; Ottolenghi et al. 1974) and nickel oxide (NTP 1996a) have resulted in lung cancer in rats exposed by inhalation. In mice, there was no evidence of a carcinogenic effect of nickel subsulfide in either sex (NTP 1996b), no evidence of a carcinogenic effect of nickel oxide in males (NTP 1996a), and equivocal evidence of carcinogenic activity of nickel oxide in females (NTP 1996a) based on the observation of alveolar/bronchiolar adenomas and carcinomas. Although nickel sulfate was the most toxic, it was not carcinogenic in either rats or mice (NTP 1996c).

2. HEALTH EFFECTS

Cancer was not observed in animals after chronic oral exposure to nickel (Schroeder and Mitchener 1975; Schroeder et al. 1964), and because absorption of nickel following oral exposure is limited, cancer following oral exposure to nickel is unlikely. Carcinogenicity studies using animals dermally exposed to nickel were not located. Cancer has been observed, however, after parenteral administration of less-soluble nickel compounds (e.g., nickel oxide, nickel subsulfide) but not soluble nickel compounds (Gilman 1962; Kasprzak et al. 1983; Lumb and Sunderman 1988; Smialowicz et al. 1985; Sunderman and Maenza 1976; Sunder-man and McCully 1983).

Genotoxicity. Investigators conducting epidemiology studies have reported a higher incidence of chromosomal aberrations in nickel workers compared to controls (Elias et al. 1989; Waksvik and Boysen 1982). Both *in vitro* and *in vivo* studies in mammals indicate that nickel is genotoxic (Andersen 1983; Biedermann and Landolph 1987; Conway and Costa 1989; Costa et al. 1982; DiPaolo and Casto 1979; Hansen and Stem 1984; Larramendy et al. 1981; Miura et al. 1989; Ohno et al. 1982; Saxholm et al. 1981; Sobti and Gill 1989; Wulf 1980), and the mechanism of action of nickel on cellular DNA has been studied (Ciccarelli and Weterhahn 1982; Patiemo and Costa 1985, 1987; Robinson and Costa 1982). Additional studies regarding the genotoxicity of nickel compounds are not needed at this time.

Reproductive Toxicity. An increase in the abortion rate has been reported among women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). The contribution of heavy lifting and possible heat stress to this effect is not known. A number of studies suggest that high doses of nickel can result in testicular effects (Benson et al. 1987, 1988; Hoey 1966; Kamboj and Kar 1964; Mathur et al. 1977; Sobti and Gill 1989). Following inhalation exposure, the investigators (Benson et al. 1987, 1988) considered the testicular effects to be secondary to emaciation. From the results of animal reproductive studies following oral exposure to nickel (Ambrose et al. 1976; RTI 1988a, 1988b; Smith et al. 1993) it was concluded that high doses of nickel result in difficulties in producing viable post-weaning offspring. The principal effects noted include maternal deaths at parturition and deaths of pups during the lactation period. An intravenous study in rats suggests a nickel effect on the release of prolactin by the pituitary (LaBella et al. 1973). Nickel treatment of rats during lactation has also been shown to change the quality of the milk (Dostal et al. 1989). Further studies concerning the role of physiological levels as well as toxic levels of nickel in the release of prolactin from the pituitary should

shed some light on the reproductive and developmental effects of nickel and may help explain the relative lack of dose response observed in the reproductive studies.

Developmental Toxicity. An increase in structural malformations was observed in infants of women who worked in a nickel hydrometallurgy refining plant in the arctic region of Russia (Chashschin et al. 1994). The contribution of heavy lifting and possible heat stress to this effect is not known. Decreased fetal body weight was observed in offspring of rats exposed to high levels of nickel via inhalation during gestation (Weischer et al. 1980). Developmental effects such as increased pup mortality and decreased pup body weight in multigeneration and multilitter studies in rats were observed following oral exposure to high levels of nickel (Ambrose et al. 1976; RTI 1988a, 1988b; Smith et al. 1993). A cross-fostering experiment may help determine if the deaths during weaning are a result of a defect in the offspring or a result of poor nutrition from changes in milk quality or quantity. Studies assessing the developmental effects following dermal exposure were not located. Developmental effects have also been observed in animals following parenteral administration of nickel (Chemoff and Kavlock 1982; Lu et al. 1979; Sunder-man et al. 1978).

Immunotoxicity. Humans have been shown to develop sensitivity to nickel (Bencko et al. 1983, 1986; Mozzanica et al. 1990). Oral challenge with a single dose of nickel has been found to elicit nickel dermatitis in sensitized individuals (Burrows et al. 1981; Gawkrodger et al. 1986; Kaaber et al. 1978; Nielsen et al. 1990), although intermediate-duration oral nickel exposure can reduce dermatitis in some sensitive individuals (Santucci et al. 1994; van Hoogstraten et al. 1994). A study that showed a reduction in the risk of sensitivity if orthodontic treatment preceded ear piercing, and the observation that mice could only be sensitized if oral nickel exposure was low (van Hoogstraten et al. 1991), suggest that oral nickel exposure before a sensitizing exposure may help prevent sensitivity. Further studies concerning the prevention of nickel sensitivity in humans should be undertaken. Studies further assessing the cross-sensitization of nickel with other metals would also be helpful. A battery of immune function tests would further assess the immunotoxicity of nickel in humans and animals.

Neurotoxicity. Neurological effects (giddiness, weariness) have been observed in workers who drank water from a. nickel/boric acid-contaminated drinking fountain (Sunderman et al. 1988), and temporary blindness in half of each eye occurred shortly after one person took a 0.05-mg/kg dose of nickel as nickel sulfate in drinking water (Sunderman et al. 1989b). No studies were located

regarding neurological effects in humans after inhalation or dermal exposure. No studies regarding neurological effects in animals after inhalation exposure to nickel were located. Neurological signs (lethargy, ataxia, prostration) were observed in dying rats treated with nickel for 3 months; however, these effects were probably associated with overall toxicity (American Biogenics Corporation 1988). Injection studies have shown that nickel can decrease body temperature (Gordon 1989; Gordon et al. 1989; Hopfer and Sunderman 1988; Watanabe et al. 1990). Because nickel also disturbs the circadian rhythm of temperature regulation, this decrease is thought to resul from an effect on the central nervous system. Further studies concerning the ability of nickel ions to replace calcium ions in the nervous system may provide insight into the mechanisms of nickel neurotoxicity.

Epidemiological and Human Dosimetry Studies. Epidemiology studies regarding nickel toxicity are available in the literature (Chovil et al. 1981; Cornell and Landis 1984; Cox et al. 1981; Cragle et al. 1984; Doll et al. 1977; Enterline and Marsh 1982; Kilbum et al. 1990; Magnus et al. 1982; Polednak 1981; Redmond 1984; Shannon et al. 1984a, 1984b, 1991; Sunderman et al. 1988, 1989a). These studies mainly focus on occupational exposure and on individuals who have been sensitized to nickel. The International Committee on Nickel Carcinogenesis in Man (1990) reviewed all available cancer data and the associated nickel exposure data. They concluded that less-soluble nickel compounds were carcinogenic following inhalation exposure and that soluble nickel compounds may also contribute to the increased risk. Lung and nasal cancers were the only sites with increased cancer risk. As nickel exposure levels in the occupational environments have been reduced, continued monitoring of populations occupationally exposed to nickel would be useful to determine if more subtle health effects occur in humans at lower concentrations.

Biomarkers of Exposure and Effect. Nickel is a normal part of the diet, and all persons have nickel in the blood, urine, and feces. In persons exposed to nickel above background levels, positive qualitative correlations have been found between air concentrations of nickel and nickel levels in the feces (Hassler et al. 1983) and urine (Angerer and Lehnert 1990; Bemacki et al. 1978). Urinary nickel levels measured on day 4 of a 5day workweek were the most effective in monitoring nickel exposure. After reviewing monitoring data in occupationally exposed workers, Sunderman (1993) concluded nickel concentrations in body fluids should not be viewed as indicators of specific health effects. Sunderman (1993) did suggest that for persons exposed to soluble nickel compounds (e.g., nickel chloride, nickel sulfate) increased nickel concentrations in

body fluids is a signal to reduce exposure and that the absence of increased values indicates nonsignificant exposure. For persons exposed to less-soluble nickel compounds (e.g., nickel subsulfide, nickel oxide), increases in nickel concentrations in body fluids indicate significant absorption, and exposure should be reduced to the lowest level attainable. In contrast to soluble nickel compounds, the absence of increased nickel in body fluids does not mean freedom from the health risks (e.g., lung and nasal cancers) that have been observed following occupational exposure to less-soluble nickel compounds.

A relationship between human lymphocyte antigens and nickel sensitivity exists and predicts that individuals with this antigen have a relative risk of approximately 1 in 11 of developing nickel sensitivity (Mozzanica et al. 1990). Antibodies to hydroxymethyl uracil, an oxdized DNA base, have also been shown to be increased in some nickel-exposed workers (Frenkel et al. 1994). A preliminary study using imaging cytometry of nasal smears obtained from nickel workers indicates that this method may be useful to detect precancerous and cancerous lesions (Reith et al. 1994). Studies that identify nickel-specific biomarkers may be helpful in alerting health professionals to nickel exposure before serious toxicological effects occur.

Absorption, Distribution, Metabolism, and Excretion. Pharmacokinetic studies in humans indicate that nickel is absorbed through the lungs (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991), and gastrointestinal tract (Sunderman et al. 1989b), and into the skin (Fullerton et al. 1986; Norgaard 1955). Food greatly decreases the adsorption of nickel from the gastrointestinal tract (Sunderman et al. 1989b). Following absorption from the lungs and the gastrointestinal tract, nickel is excreted in the urine (Angerer and Lehnert 1990; Bemacki et al. 1978; Elias et al. 1989; Ghezzi et al. 1989; Hassler et al. 1983; Sunderman et al. 1989b; Torjussen and Andersen 1979). Increased levels of nickel were found in the lungs, nasal septum, liver, and kidneys of workers inhaling nickel (Kollmeier et al. 1987; Raithel et al. 1988; Rezuke et al. 1987; Sumino et al. 1975; Torjussen and Andersen 1979). Animal data indicate that after inhalation, nickel particles can remain in the lungs (nickel oxide) or be absorbed and then excreted in the urine (nickel sulfate). High levels of nickel have been found in the liver, kidneys, and spleen of animals after inhaling high levels of nickel (Benson et al. 1987, 1988; Tanaka et al. 1985). Nickel that has been absorbed after oral exposure is primarily distributed to the kidneys before being excreted in the urine. High levels of nickel were also found in the liver, heart, lungs, fat, peripheral nervous tissue, and brain (Ambrose et al. 1976; Borg and Tjalve 1989; Dieter et al. 1988; Jasim and Tjalve

1986a, 1986b; Oskarsson and Tjalve 1979; Whanger 1973). Studies examining the bioavailability of nickel from soil following oral exposure would be useful for determining the absorbed dose from nickel-contaminated soil at a hazardous waste site. Further verification of the toxicokinetic model developed by Sunderman et al. (1989b) would improve the ability to predict the absorbed dose following oral exposure.

Comparative Toxicokinetics. Studies that examine the toxicokinetics of nickel in humans after occupational exposure, ingestion of nickel from food and water, and dermal exposure are available (Bennett 1984; Fullerton et al. 1986; Grandjean 1984; Norgaard 1955; Sunderman and Oskarsson 1991; Sunderman et al. 1989b). The toxicokinetics of both inhaled and ingested nickel have been examined in several species of animals (rats, mice, dogs, hamsters) (Ambrose et al. 1976; Benson et al. 1987, 1988; Borg and Tjalve 1989; Dieter et al. 1988; Dunnick et al. 1989; Jasim and Tjalve 1986a, 1986b; Oskarsson and Tjalve 1979; Tanaka et al. 1985; Whanger 1973). Dermal studies have been performed in guinea pigs and rabbits (Lloyd 1980; Norgaard 1957). The limited human data correlate well with the toxicokinetics observed in animals. Studies that compare the toxicokinetics of humans and animals using the same experimental protocol would be helpful in determining which species of animal is the best model for assessing the effects of nickel in humans.

Methods for Reducing Toxic Effects. Approximately 20-35% of inhaled less-soluble nickel is absorbed through the lungs (Bennett 1984; Grandjean 1984; Sunderman and Oskarsson 1991). Methods that would enhance the clearance of nickel from the lung, thus preventing or reducing the severity of lung damage (inflammation or fibrosis), would be useful. The administration of EDTA in food (Solomons et al. 1982) and the presence of food in the stomach (Christensen and Lagesson 1981) decrease the amount of nickel that is absorbed through the gastrointestinal tract. Several chelating agents (e.g., TETA, Cyclam, EDTA) have been shown to be effective in reducing the body's nickel burden (Horak et al. 1976; Misra et al. 1988; Sunderman et al. 1976). It is not known if other methods, such as dialysis, would be more effective in reducing the body burden. The mechanism of nickel toxicity involves the binding of nickel ions to macromolecules; chelating agents have been shown to bind to the nickel ions, thus mitigating the toxicity. Studies designed to determine if other methods would be more effective in binding nickel ions would be useful.

2.10.3 On-going Studies

A number of on-going studies were identified in the CRIS (1994) and FEDRIP (1994) databases. F. Nielsen and coworkers are continuing work on the biochemistry and metabolism of nickel. The mechanism of nickel carcinogenesis is being studied by E. Snow, M. Costa, I-N Chou, K.S. Kasprzak, and D.E. Wilcox. J.N. Forrest is studying the effect of nickel on signal transduction using the shark rectal gland as a model. E.A. Lefurgey is studying the effect of nickel on prolactin, growth hormone, and thyroid stimulating hormone release in female rats treated with nickel chloride in the drinking water before mating and throughout pregnancy.

The Nickel Producers Environmental Research Association (NiPERA) is sponsoring research to develop toxicokinetic models to be used to predict health effects in humans and is comparing the toxicokinetic properties of nickel in various animal species.